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SELF-ASSEMBLING GENES, VECTORS AND USES THEREOF

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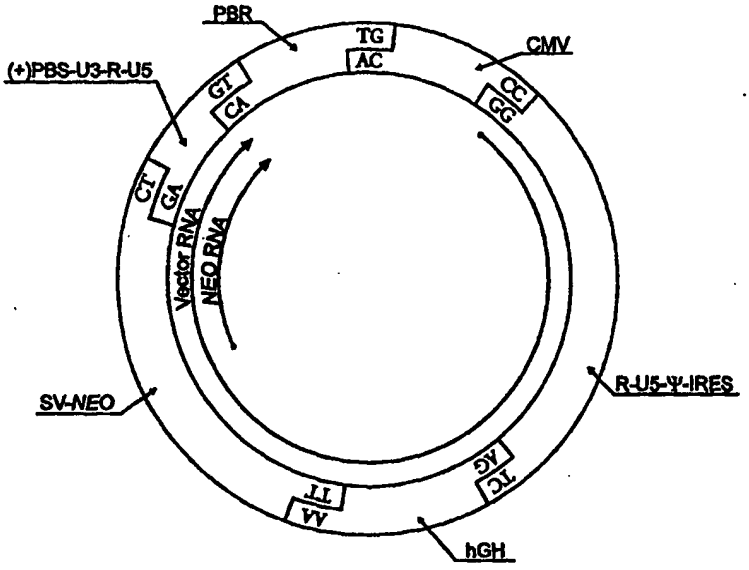

(57) Abstract

The invention relates to a method for directing the self–assembly of a gene or gene assembly having three and preferably six or more fragments in a directionally and spatially ordered fashion to produce a gene, gene vector or large nucleic acid molecule. The method can be used to create libraries, such as combinatorial libraries. In another embodiment of the invention a vector is described for the incorporation and screeming of endogenous mouse promoter elements for the identification of cell–specific promoters.

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SELF-ASSEMBLING GENES, VECTORS AND USES THEREOF

Field of the Invention

This invention relates to the construction and usage of synthetic genes for genetic engineering and gene therapy.

Background of the invention

This application claims the benefit of a provisional application U.S. Serial No. 60/070,910, filed on February 28, 1997, entitled "Self-Assembling Genes."

Recombination at the genetic level is important for generating diversity and adaptive change within genomes of virtually all organisms. Recombinant DNA technology is based upon simple 'cut-and-paste' methods for manipulating nucleic acid molecules *in vitro*. The pieces of genetic material, or DNA are first digested with a restriction endonuclease enzyme which recognizes specific sequences within the DNA. After preparation of two or more pieces of DNA, the ends of the DNA are further manipulated, if necessary, to make them compatible for ligation or joining together. DNA ligase, together with adenosine triphosphate (ATP) is added to the genes, ligating them back together. The genetic assembly containing an origin of DNA replication and a selectable gene is then inserted into a living cell, is grown up, and is positively selected to yield a pure culture capable of providing high yields of individual recombinant DNA molecules, or their products such as RNA or protein.

Significant improvements have been made to this technology over the last two and a half decades. Numerous enzymes, end-linkers and adapter molecules have been made commercially available, which facilitate in the construction of recombinant DNA molecules. By using two restriction enzymes with different single-stranded termini or blunt ends, it is possible to directionally assemble genes (forced cloning). This reduces the amount of screening required to determine orientation. Procedures have been automated for synthesis of single-stranded gene fragments up to 200 or more nucleotides in length by means of phosphoramidite chemistry, and the instrumentation is readily available through Applied Biosystems, Inc., Foster City, CA. Such single-stranded fragments can be joined by annealing overlapping complimentary phosphorylated strands, and by enzymatically filling in the ends with DNA polymerase and DNA precursors. In this way, multiple, overlapping, single-stranded fragments can be assembled into a larger, double-stranded superstructure.

Whole genes have been synthesized by similar methods. However, it becomes increasingly difficult to use synthetic DNA strands when making genes larger than approximately one kilobase. Using gene amplification methods (e.g. polymerase chain reaction (PCR), Mullis *et al.*, U.S. Patent 4,683,195), together with synthetic oligonucleotides, it is possible to make biologically active, synthetic retro-vectors that are capable of RNA transcription, reverse-transcription, viral packaging, and integration into genomic DNA (see for example, Hodgson, WO94/20608). Hodgson, *supra*, also disclosed methods for cloning of transcriptional promoters into such a vector using traditional recombinant DNA technology.

Modified restriction enzyme sites, linkers, and adapters can change the primary or secondary structure of complex nucleic acid sequences thereby altering or obliterating a desired biological activity. For example, small mutations can drastically modify transcriptional promoters or change the reading frame of coding DNA. A logical goal of vectorology is to make exact constructs, without need of fortuitous restriction sites, adapters, or linkers.

Restriction endonucleases can be grouped based on similar characteristics In general there are three major types or classes: I, II (including IIS) and III. Class I enzymes cuts at a somewhat random site from the enzyme recognition sites (see Old and Primrose, 1994. *Principles of Gene Manipulation.* Blackwell Sciences, Inc., Cambridge, MA, p.24). Most enzymes used in molecular biology are type II enzymes. These enzymes recognize a particular target sequence (i.e., restriction endonuclease recognition site) and break the polynucleotide chains within or near to the recognition site. The type II recognition sequences are continuous or interrupted. Class IIS enzymes (i.e., type IIS enzymes) have asymmetric recognition sequences. Cleavage occurs at a distance from the recognition site.

These enzymes have been reviewed by Szybalski et al. *Gene* 100:13-26, 1991. Class III restriction enzymes are rare and are not commonly used in molecular biology.

U.S. Patent No. 4,293,652 employed a linker with a class IIS enzyme recognition sequence to permit synthesized DNA to be inserted into a vector without disturbing a recognition sequence. Brousseau et al. (*Gene* 17:279-289, 1982) and Urdea et al. (*Proc. Natl. Acad. Sci. USA* 80:7461-7465, 1983) disclose the use of class IIS enzymes for the production of vectors to produce recombinant insulin and epidermal growth factor respectively. Mandecki et al. described a method for making synthetic genes by cloning small oligonucleotides using a vector (*Gene* 68:101-107, 1988). Expansion of a population of

oligonucleotides required synthesis, cloning excision and fragment purification. The oligonucleotides were used to create a complete plasmid.

Lebedenko et al. (*Nucl. Acids Res.* 19(24):6757-6771) illustrated the class IIS enzymes and PCR for precisely joining 3 nucleic acid molecules for convention sub-cloning using BamHI. Tomic *et al.* (*Nucleic Acids Res.*, 18:1656, 1990), reported a method for site-directed mutagenesis using the polymerase chain reaction and class IIS enzymes to join two nucleic acid molecules. Two overlapping PCR primers were used where the primers included class IIS recognition sites. The primers included a region of complementarity to the template DNA and include one to a few site-directed mutations. Stemmer et al. (U.S. Patent No. 5,514,568) employed overlapping primers with class IIS enzymes to amplify a plasmid and to introduce specific mutations into DNA leaving all other positions unaltered.

There remains a need for the ordering and assembly of complex genes to overcome the problems associated with sequential sub-cloning such as multiple purification steps, the potential for sample loss, and the like. Moreover there is a need for eliminating the use of prokaryotic hosts and for minimizing or avoiding the risks associated with bacterial contamination resulting from the use of bacteria as intermediaries in the cloning process. Further, there remains a need for efficient methods to assemble large nucleic acid molecules or many-fragmented nucleic acid assemblies with precision.

Brief Description of the Figures

Fig. 1A. provides one schematic of six double stranded DNA fragments, each terminus comprising a unique overhanging two-nucleotide sequence complementary to only one other terminus

Fig. 1B. illustrates a three-piece ligation where 100% of the clones tested contained the predicted fragment order and desired fragment orientation.

Fig. 2. illustrates the use of a class IIS restriction endonuclease (as one example, *Bpm*1), restriction endonuclease recognition site and the selection of cohesive overhanging ends.

Fig. 3A. illustrates an exemplary retrotransposon-derived vector including a murine VL30 LTR (NLV-3) and packaging signal, an internal ribosome entry site (IRES) from encephalomyocarditis virus (EMCV), a gene encoding a green fluorescent protein (GFP), additional internal VL30 sequences (solid bar), SV40 early region promoter and Tn5

aminoglycosidase phosphotransferase (neo) gene, PBR322 plasmid origin of replication and a plus-strand primer binding site (VL30). An exemplary vector sequence is provided as VLBPGN (SEQ ID NO:1). Fig 3B is an illustration of an LTR with the insertion of a U3 (transcriptional promoter)region rescued by reverse transcriptase-polymerase chain reaction (RT-PCR). The promoter is amplified from the RNA of a cell expressing the VL30 U3 region. Complementary overhanging ends are created using class IIS restriction endonuclease digestion sites within the LTR and within the promoter. Fig. 3C provides the linear structure of a VL30 RNA transcript from a mouse cell with a U3 region near the 3'-terminus of the RNA molecule. PCR primers include a class IIS enzyme recognition site to amplify the U3 region from the RNA resulting in a double stranded DNA molecule. Cleavage with a class IIS enzyme (here *Bpm*I), results in a double-stranded DNA molecule with end complementary to a site in the vector of Fig. 3A.

Fig. 4A. is a schematic illustrating steps for assembling a combinatorial library of *cis*- or *trans*-acting nucleic acid sequences for assembly and screening, useful for the rescue of biologically active species. Fig. 4b is a diagram of a U3 (transcriptional enhancer and promoter region of an LTR illustrating several sub-divisions of the transcriptional control region, including a distal enhancer region, an enhancer repeat region, a medial promoter and a proximal promoter. These regions have been described for other vectors in Hodgson et al. (1996. "Construction, Transmission and Expression of Synthetic VL30 Vectors" in Hodgson ed. *Retro-vectors for Human Gene Therapy.* RG Landes Company, Austin TX). Segments of these regions are amplified using primers for highly conserved sequences. Highly conserved sequences are determine based on a comparison of known VL30 sequences such as provided in Fig. 4.2 of Hodgson, 1996, *infra*). The parts are joined by annealing and ligation to provide an ordered assembly. Each construct is an allele or a representative of allelic variation in the combinatorial library.

Fig. 5 discloses two transcriptional promoters that have been rescued from mouse VL30 RNA sequences isolated from a mouse T-helper cell library. These promoters were assembled into a vector andintroduced into retroviral helper cells and packaged into recombinant retrovirus for introduction into human T-cells. After transduction to human T cells, a β-galactosidase reporter gene was expressed from the T cell-derived promoters.

Fig. 6 discloses 10 biologically active mouse VL30 promoters obtained from mouse liver RNA. These promoters were introduced into the vector of SEQ ID NO:1. The vectors

were introduced into retroviral helper cells and then packaged into retrovirus where they were introduced into human liver cells. The cells expressed the green fluorescent protein.

Fig. 7 illustrates a similarity plot of nucleotide sequences found in VL30 U3 regions.

Fig. 8 illustrates a retro-vector comprising six double-stranded DNA fragments that were self-assembled into a circular structure using unique overlapping termini created using class IIS restriction endonucleases. Three templates and twelve primers were used in conjunction with three class IIS enzymes to make the six fragments that were ligated in a single step. The vector was efficiently self-assmebled and was effectively transmitted by both DNA transfection as well as by retroviral transduction of the self-assembled DNA, without molecular cloning through a prokaryotic host (see Example 2).

BRIEF SUMMARY OF THE INVENTION

The invention described herein provides seamless, directional, ordered construction of complex DNA molecules, vectors and libraries. More particularly, it enables gene constructs to be assembled with greater efficiency and precision, and it enables multiple gene fragments to be assembled in the correct order and orientation without disturbing the internal structure of the gene. The method utilizes *in vitro* assembly of nucleic acid fragments and relies upon the unusual ability of certain enzymes to digest nucleic acid molecules at pre-determined sites without disrupting the structure of the gene. It is especially useful for the construction of genetic vectors for gene therapy or genetic engineering of cells and organisms. A particular application of the invention is in combinatorial, or evolutionary genetics, where it enables a large number of non-random, self-assembled constructs to be screened simultaneously for function.

In a preferred embodiment of this invention, the invention relates to a method method for assembling a gene or gene vector comprising the steps of: a) designing at least 6 primers to produce to amplify at least three fragments in at least three separate polymerase chain reactions wherein each primer comprises at least one predetermined restriction endonuclease recognition site that recognizes a restriction endonuclease that cleaves at a distance from the recognition site, a sequence complementary to a template nucleic acid for amplification, and bases positioned at the restriction endonuclease cleavage site that are selected to be complementary to only one other overhanging created from enzymatic cleavage of the fragments; b) combining the primers with template nucleic acid and performing the

polymerase chain reaction to produce multiple copies of an amplified template fragment incorporating the restriction endonuclease recognition site; c) digesting the amplified template fragments with one or more restriction endonucleases that recognize the restriction endonuclease recognition site of the primers to create overhanging termini wherein each overhanging termini is complementary to only one other overhanging termini on another fragment; and d) combining the amplified and digested template fragments in a ligation reaction to produce a directionally ordered gene, nucleic acid fragment or gene vector.

In a preferred aspect of this embodiment, the restriction endonuclease is at least one class IIS restriction endonuclease and preferably, the class IIS restriction endonuclease is selected from the group consisting of: *Alw*I, *Alw*26I, *Bbs*I, *Bbv*I, *Bbv*II, *Bpm*I, *Bsm*AI, *Bsm*I, *Bsm*BI, *Bsp*MI, *Bsr*I, *Bsr*DI, *Eco*57I, *Ear*I, *Fok*I, *Gsu*I, *Hga*I, *Hph*I, *Mbo*II, *Mnl*I, *Ple*I, *Sap*I, *Sfa*NI, TaqII, *Tth*111II. Still more preferably, class II restriction endonuclease recognition sites (to be distinguished from class IIS restriction endonuclease recognition sites), linkers, or adapters are not used to create the gene or gene vector. In one embodiment, the product of the ligation reaction is introduced into prokaryotic or eukaryotic cells. Preferably, at least one template nucleic acid sequence is chosen from the group consisting of : transcriptional regulatory sequences; genetic vectors; introns and/or exons; viral encapsidation sequences; integration signals intended for introducing nucleic acid molecules into other nucleic acid molecules; retrotransposon(s); VL30 elements; or multiple allelic forms of a sequence.

In another preferred aspect of this embodiment, the method is used to generate combinatorial libraries of a target sequence. Preferably, the target sequence is part or all of a gene. In one embodiment, the gene encodes a protein. In one embodiment, the primers amplify allelic variants of part or all of a gene.

In still another preferred aspect of this embodiment, the product of the ligation reaction is passed between eukaryotic cells using a virus particle, by cell fusion, or by transfection. Preferably the product of the ligation reaction is not introduced into prokaryotic cells. Moreover, the method further comprises combining at least one screening or selection step to select the products of the ligation reaction. In one embodiment, the product of the ligation reaction is mutated during passage in cells in order to generate genetic diversity and preferably the product of the ligation reaction is mutated by homologous recombination during passage in cells.

In another aspect of this embodiment, the method is used to isolate and identify regulatory sequences from a cell. In another aspect of this embodiment, cells containing the product of the ligation reaction are selected for enhanced biological activity. Preferably, the cells containing the product of the ligation reaction are selected for tissue-specific, hormone-specific or developmental-specific gene expression. Also preferably, the ligation reaction is a circularized gene vector.

In another embodiment of this invention, the invention relates to a nucleic acid primer having a 5' and a 3' end to amplify a nucleic acid fragment for the ligation of at least two fragments comprising: a restriction endonuclease recognition site that recognizes a restriction endonuclease, wherein the restriction endonuclease cleaves at a distance from the recognition site and creates overhanging termini; a sequence complementary to a template sequence to be amplified to produce the nucleic acid fragment; at least two nucleic acid bases positioned at the restriction endonuclease cleavage site and that form an overhanging terminus after cleavage by the restriction endonuclease, wherein the at least two nucleic acid bases are selected to be complementary to only one other overhanging terminus on another fragment of the ligation; and an affinity handle on the 5' end of the primer. Preferably the primer further comprises an anchor to provide stability to the restriction enzyme at the restriction enzyme recognition site.

In yet another embodiment of this invention, the invention relates to a method for isolating and identifying promoters comprising the steps of: a) obtaining a vector comprising at least a portion of a promoter region from a retrovirus transposon LTR and having two non-complementary overhanging termini; b) designing at least two PCR primers to amplify at least one region of a retrovirus transposon LTR from template nucleic acid to produce at least one nucleic acid fragment wherein each primer comprises at least one predetermined restriction endonuclease recognition site that recognizes a restriction endonuclease that cleaves at a distance from the recognition site, a sequence complementary to a template sequence from a retrovirus transposon, and bases positioned at the restriction endonuclease cleavage site that are selected to be complementary to only one other overhanging terminus of the vector wherein the restriction endonuclease cleavage site is created from enzymatic cleavage of the fragments; b) combining the primers with template nucleic acid and performing a polymerase chain reaction to produce multiple copies of an amplified template fragment incorporating the restriction endonuclease recognition site; c)

digesting the amplified template fragments with one or more restriction endonuclease that recognize the restriction endonuclease recognition site of the primer to create overhanging termini; and combining the amplified and digested template fragment in a ligation reaction with the vector to produce a gene vector with an intact LTR sequence. In one embodiment of this aspect of the invention, the template nucleic acid is DNA or RNA. In another embodiment of this aspect of the invention, the method further comprises the step of sequencing the insert to identify the promoter sequence. In one embodiment promoter sequences of SEQ ID NOS:1-13 identified using the methods of claim.

Detailed Description of the Invention

In one embodiment of this invention, the invention relates to the seamless, oriented self-assembly of at least three DNA fragments having overlapping unique cohesive ends generated by the enzymatic cleavage of at least one restriction endonuclease that is capable of cleaving at a site distant to the restriction enzyme recognition site. Preferably the restriction endonucleases employed in this invention are class IIS restriction endonucleases. These enzymes recognize a predetermined group of nucleotides and cleave at a distance characteristic of the particular endonuclease from the recognition site. The term "unique cohesive ends" is used herein to refer to the notion that the cleavage site for the endonucleases of this invention can be manipulated to produce overhanging ends with unique termini selected by the investigator. The term "complementary" as used herein in reference to the overhanging ends of the fragments of this invention refers to standard complementarity recognized in the field of molecular biology. For example, the nucleotides sequence 5'-TAG-3' is said to be complementary to the nucleotide sequence 5'-CTA-3'. The term "PCR" is used generally to refer to the polymerase chain reaction and its variations, including RT-PCR as well as other gene amplification techniques employing primers.

In a first step for practicing one embodiment of this invention, a series of at least three overlapping fragments are created through the selection and creation of primers incorporating at least one class IIS restriction enzyme recognition sequence. The oligonucleotide primers of this invention are designed to amplify one or more nucleic acid fragments and comprise a sequence complementary to a target sequence for gene amplification, a recognition sequence for a restriction endonuclease that cleaves DNA at a distance from the recognition sequence (such as a class IIS restriction enzyme) and bases

positioned at the restriction endonuclease cleavage site that are preferably unique and complementary to only one other overhanging termini in the annealing/ligation reaction that generates the complex nucleic acid molecules. Optionally, the primers of this invention can include an "affinity handle for cleanup" at the 5'end. These sequences can be of any length, preferably at least about 6 bp and the sequences extend the primer in the 5' direction from the restriction enzyme recognition site. This extra length gives many enzymes greater stability and improved activity. In addition, the sequence can be used for recognition and removal of the ends of the primers (either undigested fragments or digested ends of primers) using complementary nucleotide sequences bound to a solid support (such as cellulose, nitrocellulose or silica). Incubation with, or passage over a column or support containing the complementary sequences can be used to remove the tags by allowing them to anneal or hybridize. The nucleic acid can then be eluted from the column. Adapters can also be used in this invention. For purposes of this invention, adapters refer to double stranded fragments containing an enzyme recognition site, according to this invention. The adapters are ligated to double stranded DNA molecules, creating a fragment analogous to a PCR fragment with similar sites derived from a primer. The primers or adapters can be prepared using a number of methods for synthesizing oligonucleotides known in the art. For example instruments for producing oligonucleotides are available from Applied Biosystems, Inc., Foster City, CA.

In one example, for the design of an oligonucleotide primer for use in this invention, the particular complementary bases that will form the site for hybridization of the primer to template (i.e., target DNA or RNA) are selected. A restriction endonuclease recognition site is selected followed by a number of nucleotides to be positioned between the recognition site and the cleavage site. The nucleotides of the cleavage site are selected to include overhanging regions formed from the restriction endonuclease cleavage that are complementary to the overhanging regions of an adjacent fragment in the annealing/ligation reaction.

The length of the primer used in this invention can vary, but preferably the primer length is up to about 80 bases and preferably up to about 50 bases. In addition the primers are preferably at least about 15 bases in length and preferably at least about 25 bases in length. The 5' region of the primer contains preferably at least about 6, preferably at least about 10 and still more preferably at least about 16-18 bases that are not complementary to the template DNA or RNA. Further, the primer incorporates a restriction endonuclease

recognition site preferably 5' to the region of complementarity and a restriction endonuclease digestion site preferably 5' to the region of complementarity or within the region of complementarity. There are a variety of restriction endonucleases that cleave at a distance from the restriction endonuclease recognition site of a DNA strand and a variety of enzymes that are commercially available from New England Biolabs are provided in Table 1.

Table 1. Restriction endonucleases useful in the construction of self-assembling genes

Enzyme:	Site size (bp):	Distance to overlap:	Size of overlap:	Overlap type:
Alw26 I	5	1-5bp	4bp	5'-Overhang
*Bbs*I	6	2-6bp	4bp	5'-overhang
*Bpm*I	6	16-14bp	2bp	3'-overhang
*Bsm*BI	6	1-5bp	4bp	5'-overhang
*Bsp*MI	6	4-8bp	4bp	5'-overhang
*Bsr*DI	6	0-2bp	2bp	3'-overhang
*Eco*57I	6	16-14bp	2bp	3'-overhang
*Fok*I	5	9-13bp	4bp	5'-overhang
*Hga*I	5	5-10bp	5bp	5'-overhang
*Hph*I	5	8-7bp	1bp	3'-overhang
*Mnl*I	5	7-6bp	1bp	3'-overhang
*Ple*I	5	4-5bp	1bp	5'-overhang
*Sap*I	7	1-4bp	3bp	5'-overhang
*Sfa*NI	5	5-9bp	4bp	5'-overhang

In addition to the enzymes provided in Table 1, other restriction endonucleases that cleave at a distance from their restriction endonuclease recognition site include, but are not limited to, *Alw*I, *Bbs*I, *Bbv*I, *Bbv*II, *Bsm*AI, *Bsm*I, *Bsr*I, *Ear*I, *Gsu*I, *Mbo*II, *Taq*II, *Tth*111II and their respective isoschizomers. These and other enzymes are known in the art and many are available from other manufacturers. The primers can be prepared to produce either 5'-overlapping ends or 3'-overlapping ends, as long as they are both are either 5'-overlapping ends or 3'-overlapping ends and are complementary to one other set of overlapping ends.

In the case of *Bpm*1 (see Example 1), the enzyme digests asymmetrically, 14-16 bp from the 3'-nucleotide of the recognition site. The resulting cleavage has a 3'-overhanging end of 2 bp. A second primer is then designed with a complementary

overhanging end, and it is used to generate the adjoining fragment terminus. At the opposite ends of the two fragments that are to be joined, similar complementary, overhanging ends are designed.

The oligonucleotides are then combined with template nucleic acid (either DNA or RNA, e.g., such as for reverse transcriptase polymerase chain reaction (RT-PCR)) containing bases complementary to at least a 3' portion of the primers (also referred to herein as "templates"). In one embodiment, the fragments are gene-amplified by PCR, RT-PCR or another gene amplification process using established PCR protocols such as those provided with PCR amplification kits, including those available from Perkin-Elmer Corp. (Emeryville, California). Preferably, the PCR products are analyzed by electrophoresis on a gel, such as an agarose gel and still more preferably the fragments of the predicted size are purified free of excess primers and small byproducts (such as by purification through a small column, such as a Qiagen™ column (Qiagen, Valencia, CA)). Following amplification or purification, the fragments are digested with the restriction endonuclease recognizing the restriction endonuclease recognition site in the primers. The digested fragments are then purified from the digested ends of the primers, preferably by preparative agarose gel electrophoresis. The fragments are combined, annealed and are ligated using standard hybridization and ligation conditions known for cloning (see Ausubel et al., *Current Protocols in Molecular Biology*, John Wiley & Sons, 1994).

Fig. 1A illustrates an example of a self-assembling gene construct (SEQ ID NO:1) comprising six fragments, each having unique overhanging dinucleotide ends. In this example, the ends of the fragments prepared by the methods of this invention are constructed using primers that include *Bpm*I restriction endonuclease recognition sites It will be understood by those of ordinary skill in the art that one or more other restriction endonucleases (such as those of Table 1) could similarly be used for the self-assembling product of Fig. 1A. In a preferred embodiment, the primers were created as described above and preferably the 3'ends of the primers are non-palindromic (i.e., non self-complementary) to prevent self-annealing of such fragments. Each fragment in this example preferably joins to only one other dinucleotide overhang in the annealing/ligation mixture, assuring ligation only to the intended fragment partner. An advantage of this strategy is that the formation of concatamers or multimers is minimal. The restriction endonuclease site is removed by

digestion with the restriction endonuclease, leaving the junction free of the extra DNA sequences associated with the site.

Using a single restriction endonuclease with a dinucleotide overhang (for example, using the enzyme *Bpm*I) up to six pieces of genetic material can be joined together in a linear or circular form (such as a vector) without the need to perform sub-cloning procedures or detailed analysis of individual products because six unique combinations of dinucleotide overhangs create a directional clone with extremely high fidelity. With enzymes digesting single-base overlaps, only two fragments can be joined with positional and directional precision. With enzymes digesting three-base overlaps, $4^3/2$, or 32 fragments can be so joined in the correct order and orientation. Therefore, this invention also relates to the use of restriction endonuclease recognition sites that facilitate cleavage by restriction endonucleases with three-base overlaps and self-assembly gene constructs including 32 fragments. Alternatively, a combination of restriction endonuclease recognition sites for use with a combination of restriction enzymes that create two-base or three-base overlaps can be used. Each enzyme has its characteristic limits to self-assembly imposed by the size of the overlap. For example, there are sixteen dinucleotides, therefore *Bpm*I fragments (which have two dinucleotide ends each) are limited to eight for the purpose of self-assembly; therefore in another embodiment of this invention an assembly comprising eight fragments is contemplated. However, four of the sixteen dinucleotides are palindromes. Use of these palindromic dinucleotides can create some infidelity in the annealing/ligation reaction. The enzyme *Hga*I has a five base overlap, and there are 1,024 pentanucleotide combinations, permitting 512 fragments to be ligated together directionally and in order (no palindromes). The fragments to be joined at a particular place are designed to have their cut sites aligned, so that the overlapping region fits together. In some cases, the target sequences will contain natural restriction endonuclease recognition sites for the enzyme that is being used, such as one or more internal *Bpm*I sites. These sites have the potential to self-religate during vector or gene construction or they can be by passed by using a substitute enzyme in the primers (for example, Eco 571 can substitute for *Bpm*I). Alternatively, these sites can be removed by site-directed mutagenesis after consideration to the consequences of the mutagenized sequence to the gene or vector.

In addition to class IIS enzymes, class II restriction endonucleases can be used. These enzymes have intrinsic methylation activity that affects the outcome in either a

negative or a positive way, depending on the purpose for which it is used. In a preferred embodiment, the methylation activity of class II enzymes is ablated by mutation or by genetic engineering to convert the enzyme to an effective class IIS enzyme to expand the repertoire of useful enzymes for this invention.

In another aspect of this invention, the primer design and target fragment sequence selection can be automated (see Example 5) using a computer to assist in the selection of unique overhanging ends that have complementarity only to the overhanging end of an adjacent fragment.

Therefore, this invention permits high-fidelity annealing and ligation of six or more fragments with unique overhanging termini complementary to a single other overhanging termini. Any multitude of combinations can be created by combining the type of overhanging termini that can be created. Moreover, if one is willing to sacrifice the fidelity of the reaction, a variety of combinations can be used to anneal a variety of fragment numbers. In these cases, some selection may be necessary, such as size selection of the resulting fragment based on electrophoretic migration or restriction endonuclease profiling, both methods well known to those of ordinary skill in the art

It is also necessary to have a high per-step efficiency (e.g., each step in the precess is performed with an efficiency of at least 80%) to effectively ligate large numbers of fragments without error. Where large numbers of fragments are used, the purity of the fragments becomes important. This means that for large numbers of fragments, the digested DNA fragments for annealing and ligation should be substantially pure. If undigested fragments, digested ends of primers, degraded or partially degraded molecules are present, they can decrease the purity and affect the fidelity of the product. Therefore, it is particularly desirable to ensure complete digestion of both ends of each fragment and to remove al of the digested ends from the fragments prior to including the fragments in an annealing and ligation reaction. The use of Qiagen columns for oligonucleotide removal prior to digestion is generally sufficient to permit efficient digestion of the fragments. Agarose gel isolation is desirable after digestion particularly where the product contains some fragments that do not appear to be full length. The use of an analytical gel before and after digestion helps in determining whether both oligonucleotide tags have been removed. The isolation of fragments from agarose gels preferably avoids the use of ultraviolet light and exposure of the

DNA to ethidium bromide is also preferably avoided. These methods can be avoided by running replicate lanes and staining only a portion of the gel.

The fragments and vector are then digested to yield fully complementary ends, and the fragments are preferably again purified, as described above (such as through a Qiagen column or by gel isolation). The purified fragments are ligated together in a test tube, under standard conditions, such as using bacteriophage T4 DNA ligase and ATP. Preferred ligations include at least 20μg/ml total DNA concentration in the ligation mix to favor intermolecular interactions, and an equimolar ratio of fragments to be ligated. Where a prokaryotic intermediary is used, the ligated assemblage is transformed into a bacterium, such as an *E. coli* host, and the colonies are: selected with a drug (such as an ampicillin, tetracycline, or kanamycin marker). The colonies can then be selected either by individually selecting colonies or growing a mass culture, such as where a vector library has been created. Restriction enzyme analysis can be used to determine the identity of individual constructs or to assess the validation of the combination of plasmids. The plasmids can then be grown up and used as needed.

In one embodiment of this invention, at least a portion of a vector is used as one of the fragments for the ligation of at least three fragments according to this invention. In one example, where a vector is used as one of the starting fragments, two restriction endonuclease recognition sites recognizing an enzyme that cleaves at a distance from the recognition site, such as at least one *Bpm*I site, can also be introduced into the vector. This permits the vector to be digested with the restriction endonuclease to produce a product having ends complementary to two ends of the insert DNA fragments. The vector can be made by amplifying a plasmid or portion thereof using the primers of this invention. Thus, the vector can also be constructed to include a variety of restriction endonuclease recognition sites using a variety of restriction endonucleases, including a variety of class II restriction endonucleases. In some cases, the target fragments for amplification will contain natural restriction endonuclease recognition sites for the enzyme that is being used for the self-assembly, such as for example, a fragment that includes one or more internal *Bpm*I sites. Care should be taken either to utilize the complementarity of the naturally occurring site to reform the fragment as it originally existed or to eliminate the restriction endonuclease recognition site using, for example, site-directed mutagenesis. Preferably, the restriction endonuclease recognition site is be substituted for a different enzyme (in the case of *Bpm*I,

substituting *Eco*57I or *Bsr*DI) that has an equivalent structure at its ends. Two or more fragments of insert or two or more fragments of vector with at least one insert are amplified using primers according to this invention.

The exemplary enzyme, *Bpm*I digests DNA 14-16 base pairs (bp) from the 3'-nucleotide of the recognition sequence (RS). Thus, by placing the RS exactly 14-16 bp from the desired dinucleotide cut site, the practitioner tags the dinucleotide for ligation with another dinucleotide that is exactly complementary to it. Such a complementary dinucleotide can be inserted by using the same enzyme and RS to make another fragment which fits the first exactly, as illustrated in Fig. 1. Because there are sixteen possible dinucleotide combinations (including twelve combinations that do not have palindromic ends), it is possible to create up to six fragments with unique dinucleotides, and it is also possible to join them all together in a predetermined order and orientation (Fig 1A). In addition, the palindromic sequences (such as AT, CG, TA, and GC) could also be used, although inefficiency and incorrect ligation will result from the self-complimentarity of these sequences. It is furthermore possible and desirable to have three or more fragments joined in this way, such that the construct is circular as in Fig. 1, comprising a vector that may be grown in a bacterial and/or eukaryotic host cell. If the genetic construct is to be used as a vector, the vector should be designed to include a proper origin of replication to enable it to replicate in a particular cell. For example, a prokaryotic origin of replication such as a coliform plasmid origin of replication enables circular DNAs to be propagated in *E. coli* host cells. It is desirable to have at least one selectable marker, such as a neomycin marker that enables recovery of the clone through a selection process. It is also desirable, but not essential, to have two or more selectable genetic elements, to permit dual selection. For example, if one of the fragments contains a prokaryotic plasmid origin of replication, and another fragment contains a selectable marker, then the two fragments are both selectable, since the construct will grow in prokaryotic cells in the presence of a selection drug (such as ampicillin) only when both fragments are present. Drug selection can be combined with the methods of directed self-assembly to assure a high percentage of correct products. Because of the unique complementarity of the fragments, each contributes a selectable element that leads to recovery of a high percentage of correct products.

For prokaryotic vector construction, at least one fragment should contain a prokaryotic origin of replication and one fragment should contain a drug resistance marker

gene. However, an advantage of the methods of this invention is that the construct can be introduced directly into eukaryotic cells. Here no plasmid origin of replication is necessary and no prokaryotic selectable marker or other prokaryotic nucleic acid sequence is necessary. In cases where the vector is subject to regulatory approval or where optimal gene function is necessary, it may be undesirable to include prokaryotic sequences, such as extraneous plasmids or expressed prokaryotic fragments particularly if the sequences contain immunostimulatory sites that can lead to activation of the intracellular immune system and inactivation of a gene product (see Krieg et al., *J. Lab. Clin. Med.*, 128:128-133, 1996) or to avoid risks of endotoxin contamination. Moreover, the use of self-assembled product, according to the methods of this invention saves labor and time involved in the screening process.

Thus, in a preferred embodiment of the invention, the nucleic acid fragments are self-assembled *in vitro*, and are transferred directly into eukaryotic cells, by transfection, injection, or other methods known in the art. In one embodiment the cells receiving the assembled product of this invention are helper cells for recombinant virus assembly (including, but not limited to retroviral helper cells for retroviral or retrotransposon vectors, adenovirus helper cells for adenovirus vectors or herpes simplex virus helper cells for herpes simplex vectors). Alternatively, the assembled product can be introduced into cells along with a helper virus or the assembled product can be introduced into target cells for direct expression. The assembled product can be a vector, a minichromosome vector, a portion of a chromosome, or the like. In the preferred case of a retroviral vector, the genes are first transfected into a first helper cell line (such as ecotropic helper cells, GP+E86 (Markowitz et al. *J. Virol.* 862:1120-1124, 1988). The retrovirus-containing supernatant from these cells is then filtered (0.45mm Nalgene filters) preferably 48-72 hours after transfection and the filtrate is transferred to a second complementation retroviral helper cell line (such as PA317 retroviral helper cells, Miller et al., *Mol. Cell. Biol.* 6:2895-2902, 1986). After an additional 48 h, the second helper cell line is selected with the marker drug (such as the drug G418 for the selectable neomycin (neo) marker gene), until only drug-resistant cells remain. These cells contain stably integrated vectors that can be used to repeatedly transduce human cells. Advantageously, in the case of adenovirus vectors or other large eukaryotic -derived vectors including eukaryotic virus-derived vectors, it may be impossible to propagate them in prokaryotic hosts. The gene self-assembly method of the instant invention provides an

alternative to *in vitro* recombination method of gene construction by permitting large constructs to be constructed.

One advantage of introducing the assembled product of this invention into a helper cell line to produce recombinant virus for the introduction of a gene or nucleic acid complex into a cell is that the assembled product will be auto-selected by the cells during the packaging process. Therefore, even where the overhanging termini have palindromic sequences, where there is more than one (but preferably less than four) unique complementary matches for a particular overhanging termini, or where concatamers have formed, only the correct or functional assembled products are expressed, transmitted, and assembled into virus. When the virus is then introduced into cells, the use of a reporter gene or another selectable marker provides yet a second layer of security for the selection of cells containing a properly assembled construct. For example, where a retrovirus helper cell line is used to produce a recombinant retrovirus containing the product of this invention (for retrovirus, RNA transcribed from the DNA product of the invention becomes packaged into the virus particle), a retrovirus-derived vector is transcribed as RNA and transmitted by packaging the RNA in a retrovirus particle. In order to be properly transmitted as a virus, the construct must be: 1) transcribed as RNA in a vector producer cell; 2) packaged into viral particles; 3) reverse transcribed into double-stranded DNA (in the recipient cell); and 4) integrated into the host chromosome. Each of these steps requires specific *cis*-acting sequences that must be correctly positioned within the vector. Thus, passage via retrovirus (or by other virus) is a means of auto-selection for the essential sequences.

In one application of the methods of this invention, the methods are used to rescue expressed sequences from RNA, or genomic sequences from cell DNA without disrupting the promoter sequences. Cellular transcriptional promoters are typically difficult to identify and isolate because they are generally not included in the RNA molecule and often extend over a considerable distance in a chromosome. One application of this invention relates to a promoter rescue technique that permits the entire promoter, or a fragment of a promoter to be isolated and cloned directly in to an expression vector without disruption of the flanking sequences. Promoter rescue techniques are known and include WO 94/20608 to Hodgson.

In a preferred embodiment of the invention, transcriptional promoters are cloned in a transcriptionally active manner for the selection and identification of new and/or

of tissue or cell-specific promoters enabling them to be used, selected, or screened for activity directly. For example, Fig. 3 illustrates one example of the formation of a vector for the incorporation of promoter sequences and the ultimate identification of those sequences using an exemplary plasmid VLBPGN (SEQ ID NO:1) as provided in Example 3, with *Bpm*1 sites located within the locus of a retrotransposon (VL30) long terminal repeat (LTR). These methods preserve the structure and functionality of transcription factor response elements. The characteristic secondary structure of the LTR RNA remains very similar to the original LTR from which the promoter was rescued, thus preserving the important features of the original RNA/DNA molecule. Those of ordinary skill in the art will recognize that any of a variety of primers can be used with a variety of vectors and that the constructs of Figs 2 and 3 are exemplary and not limiting.

Fig. 2 illustrates the primers used to amplify the promoter insert (identified at a and c in Fig.2), and the insert region of the LTR (boxed), both of which can be digested at the same nucleotide position with *Bpm*1, to ensure a proper and seamless fit. In this example, after digestion of the vector, the two *Bpm*1 sites leave non-complementary ends (a 3'-CC overhang on one end, and a 3'-GC overhang on the other). Thus, the ends will not efficiently anneal or ligate to one another. However, the complementary termini of the insert serves as linkage, enabling the plasmid to be completed by ligation.

In the example illustrated in Fig. 2, the terminus on the 3'-side (GC) is palindromic. Palindromic termini are self-complementary and can therefore ligate to themselves or to an identical terminus facing the opposite way (forming concatamers in the opposite direction). Despite the presence of palindromic termini and despite the potential for reduced fidelity in the self-assembling process, a large percentage of clones obtained by inserting promoter sequences into VLBPGN were assembled correctly (20/23). These levels are reduced somewhat when three or more fragments are combined for self-assembly, according to this invention and preferably, the use of palindromic termini are avoided when even numbers of nucleotides are exposed as overhanging termini because with even numbers of nucleotides there is an axis of symmetry. As noted above, where five base overhangs are used there are 1024 possible combinations of five nucleotides [$(4)^5$], yet none of them is palindromic.

The vector of Fig. 3 is an example of a particular type of vector that is known as a retrotransposon vector. Retrotransposon vectors are described and reviewed in Hodgson

et al., 1996 *Retro-Vectors for Human Gene Therapy*. RG Landes Company, Austin TX, chapter 5 and see US Patent 5,354,674 to Hodgson. This type of vector is derived from a mouse cellular retro-transposon element that has no essential viral or cellular genes, and that has little sequence similarity to a retrovirus. However, this RNA (known as VL30 [virus-like, 30S]) has all the necessary *cis*-acting structural elements (such as LTRs and primer binding sites) required for efficient transmission by a type C murine or primate retrovirus. Thus, it is a parasite transmitted by retroviruses that is also expressed as a cellular RNA in most mouse cells and tissues. This RNA becomes packaged into retroviral particles when the mouse cells become infected by retrovirus. The retrovirus then transmits the VL30 (or a VL30 vector) to the next infected cell (which can be a human cell). The RNA is then reverse transcribed and integrated into the DNA of the host cell.

Some advantages of VL30 vectors (over retrovirus-derived vectors) are: 1) lack of viral genes and other sequence homology that could lead to replication competent retrovirus (RCR); 2) ability to be expressed long-term *in vivo*; 3) a variety of LTR transcriptional promoters that can be expressed in various tissues and under the influence of various hormones and other stimuli; and 4) the ability to express genes in a number of cell types that are targets of gene therapy. An additional advantage is that VL30 parts can be switched with those of classical retrovirus-derived vectors. For example, the LTR or packaging signal of VL30 can be used in place of the equivalent retroviral signal. The ability to make mixed, or chimeric retro-vectors is a special application of gene self assembly technology.

Using a specific primer set, such as that shown in Fig. 2, or others, as taught in this invention, it is possible to amplify the U3 sequences expressed in the RNA of many different types of mouse cells. This is done using standard RNA isolation methods (Ausubel *et al., supra*), coupled with extensive digestion with ribonuclease-free dexoyribonuclease, to eliminate residual DNA. Thus, to obtain a promoter that is expressed in the liver, one isolates RNA from liver and uses an RT-PCR procedure, such as those known in the art, with the primers to amplify the desired promoters. Fig. 6 illustrates liver RNA-derived promoters obtained using the methods of this invention. However, the promoters can also be derived by conventional PCR from cDNA libraries (Fig. 5 illustrates T cell-derived promoters that were obtained in this manner). It is also possible to use the well-known hormonal and pharmacological inducibility of VL30 LTRs to find LTRs that are responsive to peptides,

hormones, and cytokines (for a table and description of VL30 pharmacologic responses (see Hodgson et al., 1996 *Retro-Vectors for Human Gene Therapy*. RG Landes Company, Austin TX, chapter 4, and Fig. 4.2). Examples of substances inducing various VL30 promoters to high levels include: epidermal growth factor, basic fibroblast growth factor, insulin, erythropoietin, glucocorticoid hormones, activators of cyclic 3'-5'AMP, and others. To rescue promoters with pharmacological responsiveness, cells or animals stimulated with the desired pharmacological agent are subjected to the RT-PCR procedure and the resulting U3 regions are cloned into a vector, (such as the exemplary VLBPGN) and are tested for inducibility. Standard RNA blotting procedures can be used before isolating VL30 promoters, to determine whether a particular drug or hormone causes induction of VL30 RNA expression in a particular mouse cell or tissue. After the promoter has been rescued, the vector is transmitted via retrovirus to the target cell (possibly a human equivalent of the mouse cell from which the promoter was rescued). After selection with the drug G418 (400-700 μg/ml, for 7-10 days) to select against cells not containing the vector, the target cell population is challenged with the pharmacological agent of choice. Reporter gene expression (in the example, GFP) or RNA expression, as determined by RNA blotting, can be used as an assay of gene inducibility by the agent (for exemplary gene expression methods, see Chakraborty *et al.*, *Biochem. Biophys Res. Commun.* 209:677-683, 1995).

Using any specific primer set designed for use with VL30 retro-elements and using total cellular RNA from a particular mouse cell type as a template for RT-PCR, (using commercially available kits and methods therein) candidate promoter elements can be amplified. This method is useful for the identification of mouse-derived promoters and in particular the method is useful for the identification of cell-type specific or tissue-specific promoters from a mouse and for the selection of these promoters and the identification of tissue-specific or cell-specific promoters that function in human cells. Thus, these types of vectors and the methods for using these vectors permits the identification of promoters to permit controlled transcription of a foreign gene. The promoters, originally obtained from the mouse, can be used to effect tissue-specific or cell-specific expression in a human or animal liver cell such as a hepatocyte, or in a human blood cell such as a T-helper cell or in an erythrocyte (red blood cell). Methods are disclosed in Example 2 for the screening and selection of the promoters from a library of amplified promoter sequences. Other methods are well known to those of ordinary skill in the art. The specificity of the selected promoter

can be assessed, for example, by introducing a selectable marker under the control of the test promoter in question and introducing this construct into various cells to assess the ability of the promoter to selectively regulate expression.

The amplified fragments represent U3 promoter regions from any RNA species expressed in the originating cells and their abundance will be in approximate proportion to the number of expressed copies of RNA in the original mixture. Example 3 illustrates one example using a mouse T-helper cell cDNA library to produce amplified fragments representing U3 regions expressed in T cells. The vectors were efficiently expressed as RNA and protein in PA317 helper cells, and were transmitted by retrovirus into human T-helper cells, where they were integrated and expressed as protein in the form of a β-galactosidase reporter gene, as visualized by X-gal staining. The products of this experiment are provided in Fig. 5 and as SEQ ID NOS: 2 and 3 from T-helper RNA. The products of another experiment are shown in Fig. 6 as SEQ ID NOS: 4-13 from mouse liver RNA (by RT-PCR).

Examination of the different U3 sequences isolated from T cells and from liver revealed several things. First, the T cell U3 sequences were related to each other, as were the liver sequences. However, the two types of U3 sequences were quite different between the two sources (T-cell, Figure 5 and liver, Figure 6). Specifically, the liver sequences (Figure 6) appeared to be a closely related group, differing mostly by single point mutations, some of which may affect transcription factor binding sites. Some of the polymorphic sites included: a phorbol ester response element (VLTRE); a Rel/NFκb binding region, and a possible glucocorticoid response element (GRE). Some of these polymorphisms are illustrated in Fig. 6. The T cell-derived sequences (Fig. 5, SEQ ID NO:2 and 3), on the other hand, differed significantly in length, with SEQ ID NO:3 missing more than 120 bases (compared with SEQ ID NO:2) including putative binding sites for retinoids (RAR/RXR) and several elements contained within the enhancer repeat region (including a cAMP response element (VLCRE, or CREB/jun binding site), and putative serum response element (SRE, CARG, and NF1/IL6). SEQ ID NO:3 represented one out of five clones sequenced, while SEQ ID NO:2 represented four out of five. Possible sites of interactions between transcription factors and DNA can be observed by comparing the experimentally derived U3 sequences with those in Hodgson et al. ,(Retro-Vectors for Human Gene Therapy, 1996 Fig. 4.2 *supra*). In addition

to the deleted sequences of SEQ ID NO:2, there are a number of single base differences within the conserved regions of the two T cell-derived sequences.

Advantageously, a number of new VL30 promoter sequences (SEQ ID NOS: 2-13, *supra*) were identified using these methods despite the fact that VL30 RNA comprises only about 0.3% of cell mRNA represented in a cDNA library. Moreover, in each case, the cloned insert was isolated without the need to use linkers, adapters, or multiple cloning sequences such as those that are typically use for other library construction methods. The promoter sequences can be used in the vectors disclosed here to express inserted foreign genes or the promoter sequences can be substituted into other retroviral vectors, such as MoMLV-derived vectors or other VL30-derived vectors. Further, vectors containing the promoter sequences can be propagated in retroviral helper cells, such as PA317 (U.S. Patent 4,861,719 to Miller) or introduced into cells by chemical or physical transfection.

In another application of the methods of this invention, libraries of amplified sequences can be incorporated into vectors using two or more fragments and using the restriction endonucleases cleaving at a distance from their recognition sites. Preferably the vectors are created using six or more fragments and preferably greater than 10 or more fragments. For example, as applied to VL30 promoter sequences, because there are over a hundred VL30 retro-elements in the mouse genome, it is possible to amplify all of the promoter sequences *en masse*, and propagate them *en masse*, enabling screening by serial passage through helper cells (such as the PA317 helper cell line) or by means of a replication competent retrovirus, as illustrated in Examples 3 and 4. Conversely, the promoter region may be broken down into several sub-domains and permutations of each could be combined and screened to enhance the chances of generating a superior construct (Fig. 4B).

As an example of breaking a promoter region down into several sub-domains, Fig. 7 illustrates a similarity plot of nucleotide sequences found in VL30 U3 regions. Plot similarity was performed using the Plot Similarity program (Wisconsin Sequence Analysis Package, release 8.1, Genetics Computer Group, Madison, WI). This program plots the running average of the similarity among the sequences in a multiple sequence alignment. The sequences compared were those found in Fig. 4.2 of Hodgson, 1996, chapter 4 (*infra*). That is, the plot discloses the degree of conservation of VL30 promoter sequences among known VL30 promoters. From the figure, it can be seen that conserved sequences (close to 100% conserved) can be used as primer binding sites to amplify the adjacent sequences by PCR.

An allelic mixture of three fragment sets is then created to make a combinatorial library of promoters that can be positively selected, such as by using retroviral amplification of the active sequences. This, used in combination with the Fig. 4.2 (Hodgson, 1996, chapter 4 *supra*) can be used to determine regions of high similarity. Regions of high similarity within the U3 region can be replaced with one another. Therefore, a library of permutations of these sections can be made by combining allelic pools obtained by amplifying the sequences from individual subsections, followed by ligating the subsections in the correct order using the methods of the instant invention for gene self-assembly. For example, sub-section 1 can include the distal enhancer (from the LTR 5'-end to the site of insert primer 2, see for example the region defined by the insert primers 1 and 2 (SEQ ID NOS 55 and 56 of Example 4). In this way, using a plot similarity (such as Fig. 7), within each sub-section, the primers position fragments within a region of nearly 100% identity. Degenerate primers can also be used in these experiments to account for multiple nucleic acid base combinations along a particular sequence. In each case, the primers preferably are designed to have a melting temperature that is compatible with the RT-PCR conditions being used, and the conditions should be those recommended by the manufacturer (preferably Perkin Elmer Corp., Emeryville, CA). In Example 4, a set of primers is given that can be used to amplify different U3 subsections, together with directions for assembling a combinatorial library.

It will be appreciated by persons of ordinary skill in the art that the methods of the instant invention can thus be used to make allelic libraries of a variety of genes. For example, different allelic portions of a gene can be combined in a predetermined order and orientation to produce combinatorial libraries, without the need for fortuitous restriction sites separating the parts in the original construct, and without perturbing the important sequences joining the parts using the methods of this invention.

In this invention primers are constructed as described above. However, for the generation of allelic libraries or more complex library constructs it may be helpful to include 5'tags into the 5' end of the primer. The purposes of the tag sequence are: 1) to provide extra nucleotides on both sides of the restriction endonuclease recognition sites (for more efficient digestion); and 2) to enable recovery of sequence tags or undigested fragments by means of an affinity reagent (such as silica, magnetic beads, or nitro-cellulose containing the complementary sequences) for purification. The use of an affinity reagent permits the digested ends to be purified away from the digested fragments. Furthermore, if any

undigested ends remain after thorough digestion, the affinity reagent will remove them, further aiding in the purification. In one embodiment, affinity purification of the digested fragments is used in place of gel isolation, eliminating possible damage caused by ultraviolet light as well as possible damage caused by dye (e.g., ethidium bromide) binding to the DNA.

It will also be appreciated that a number of other variations to the primer sequences can be employed. For example, as discussed above, the enzyme recognition site for an enzyme that digests outside of its recognition sequence is included in the primer, so that the DNA digest creates an overlapping end that is complementary to one other terminus to which it will be joined. The enzyme recognition site can be moved to any location within the primer so as to digest the DNA at the exact location desired. The primer can also be programmed with a novel enzyme recognition sequence to add any desired sequences between the two sequences to be joined or to incorporate a linker or adapter if desired. If the sequences to be amplified contain the enzyme recognition site of the primers, it may be necessary to switch to a different enzyme usage. The use of several different enzymes is possible and has been discussed above. As with other PCR procedures, after the initial primer selections have been made the primers are assessed for their ability to fold back on themselves or to create internal secondary structure. The primers are preferably modified to avoid palindromic sequences or the potential for self folding within a primer. Nucleic acid analytical software (such as the Wisconsin GCG package, Oxford Biomolecular, Oxford, UK) is available to perform this analysis and aid in the selection of alternative primers.

In addition, as with all PCR processes, it is necessary to determine the melting temperatures (T_m), and to adjust the annealing temperature of the PCR reactions to compensate for such temperatures. Finally, it is important to perform a sequence redundancy search, to determine whether the target sequence (the sequence complementary to the primer) is found more than once in the region to be amplified. If the sequence is repeated, it will be necessary to use a different primer in order to establish the single, correct priming site. Preferably, no more than 6-8 bases of incorrect target complementarity at the 3'-end of the complementary region is used and to allow a difference of at least 10° C between the T_ms of the correct and the incorrect target. The annealing temperature should always be at least 5°C lower than the T_m of the correct target and 5°C above the T_m of the incorrect target. Again, the necessary software and instructions are readily available from the cited sources (Wisconsin Gene Computer Group and Oxford Biomolecular, *supra*)

Next, a vector is constructed to include the appropriate elements for expression in the desired cell type. For example, the plasmid of Fig. 3A can be used for the creation of a promoter library or a vector can be created using a commercially available vector and primers to create a three or more fragment annealing and ligation reaction as provided above. Preferably, the inclusion of a dominant negative selectable marker on the vector (*e.g.*, the neomycin phosphotransferase gene, conferring G418 drug resistance) can be used to reduce the likelihood that cells without the vector are being maintained in culture.

Multiple allelic copies of DNA (cell derived or cDNA) can be amplified in separate reactions as a set of potential inserts with each set having its own unique overlap sequence following digestion with a restriction endonuclease, according to this invention. The fragments can then be ligated into an existing vector or in a single reaction of three or more fragments to form a combinatorial collection of potential alleles. For example, if six adjacent regions are amplified from five separate alleles, the number of combinations would be 5^6, or 15,625 potential combinations. The combinations can then be grown *en masse*, and selected *in vitro* or *in vivo*. A variety of screening strategies can be used in this invention and those of ordinary skill in the art will appreciate that the type of screen will match the type of library being generation. Therefore, for the promoter library, introducing members of the library into particular cell types to assess for expression in one or more cell types versus the absence of expression in another cell type is evidence of tissue-specific or cell-specific expression. For screening purposes, the libraries of this invention function like other libraries created through other methods. A variety of screening methods for a variety of libraries have been described in the art. For example, selective screens are reviewed by Hodgson et al. (1996, RG Landes Company, *supra*). Reporter protein production is well known in the art as is dominant selectable marker (e.g. drug) selection and selection by fluorescence activated cell sorting, antibody affinity selection, phage display selection (such as commercially available from Amersham, Milwaukee, WI), and the like can be used without detracting from this invention.

In this way, it is possible to isolate multiple forms of genes, gene fragments or regulatory regions such as transcriptional promoters or packaging signals (for example, in a retro-vector system). The individual constructs may then be tested *in vitro* or *in vivo* to further characterize a particular phenotype.

In one example the method is used to create a library of complementarity determining regions (e.g., allelic variations that give rise to antibody diversity) of antibodies or from receptors, including T-cell receptors, epitopes, antigens, ligands and the like. For example, where a library of T-cell receptors is created, the introduction of a vector designed to create a functioning T-cell receptor can be introduced into T cells or T-cell progenitors and the cells can be tested for their ability to bind to a particular test ligand. The ligand-recognizing cells can then be isolated from the ligand and grown in the presence of cytokines to produce specialized T cell clones. Where a library of antibodies or antibody fragments is created, the antigen reactive portions, for example, can be recombined in a vector containing the remaining portions of an antibody molecule to generate antibodies or antibody fragments in a cell. In other examples, the methods of this invention can be used to create allelic domains of receptor families (such as the steroid receptor super-family); libraries with related regions from peptide hormones; cytochromes P450; or other protein families that have shared domains or sub-sections with similar structures. The methods of the instant invention allow the joining of allelic sub-sections in an ordered fashion. In each case, it will be necessary to design primers, and to keep track of the uniqueness of joining overlaps and the presence of internal restriction sites as described above. While these will be different in each case, here are listed some general guidelines that are incorporated into the method of the instant invention.

As discussed above, although described as it relates to promoter libraries, libraries of other nucleic acid sequences can be created using the methods of this invention. These libraries include, introns and/or exons and/or functional domains libraries, libraries of potential alleles for a particular gene sequence, and the like. These sequences can be amplified from cell DNA or RNA using the primers of this invention and incorporated into a variety of vectors. For example, one vector of this invention, VLBPGN, has a portion of LTR removed and can be used to create a variety of libraries following digestion with *Bpm*1.

Selected or screened products of the combinatorial library can be used for gene expression, such as the promoters of Figs. 5 and 6. In addition, the exploitation of these sequences for the expression of a variety of genes, the LTR fragment containing the promoter can be joined to one or more functional retroviral packaging signals, internal ribosome entry sites, additional promoters, coding regions, processing sites, and the like.

Advantageously, there are almost no spatial constraints upon the joining of molecules by the method of the instant invention and other methods have not taken advantage of the combination of PCR to isolate genes or gene fragments; enzymes cleaving at a site distant from their restriction endonuclease recognition site to combine three or more fragments with precision; and, the use of unique overlapping non-palindromic termini to ensure fidelity of multi-fragment ligations. This combination permits the artisan to prepare complex gene constructions in one ligation step and does not require sequential sub-cloning into a vector or propagation in a prokaryotic host. Added to this the combination by these methods of fragment pools facilitates recombinatorial genetics.

The ability to recombine (in the correct order and direction) and screen a large number of allelic variants (whether as a simple library or as a combinatorial library), resulting in increased abundance (by amplification in the RNA, and subsequently in the DNA) is a special characterisitic of this invention. Particular advantages of this system are obtained when the methods of this invention are combined with retrovirus vector technology or other virus vector technology. For example, the combination provides a form of *in vitro* evolution whereby the passage of the library through virus and through cells selects functioning sequences and increases the abundance of the surviving RNA and DNA molecules.

For example, consider the consequences of screening several different promoters expressing RNA in a donor cell (*i.e.*, a cell producing virus particles), but at differing levels of RNA abundance. In the following example, the least abundant RNA species is expressed at 0.1 copy of RNA per cell, while six others are expressed at 1 copy, 10 copies, 100 copies 1,000 copies, or 10,000 copies, or 100,000 copies/cell, respectively. After a single passage, the DNA copy number in the recipient cells now reflects the approximate RNA copy number in the donor cells. These numbers are further amplified in the relative abundance of RNA species produced in the recipient cells. Disallowing for factors such as position effects, transcription factor depletion, etc., (which may be considerable), the same relative ratios of expression would be expected. Taking into consideration position effects, the disparity between abundance caused by changing insertion loci should average out. The most abundant RNA species after two passages is then many orders of magnitude more abundant than the least abundant.

Species:	RNA abundance: P=0	DNA copy no. P=1	RNA abun. P=1	DNA copy no. P=2	RNA abun. P=2
A	0.1 copy/cell	0.1	0.01	0.01	0.001
B	1	1	1	1	1
C	10	10	100	100	1,000
D	100	100	10,000	10,000	10^6
E	1,000	1,000	10^6	10^6	10^9
F	10,000	10,000	10^8	10^8	10^{12}
G	100,000	100,000	10^{10}	10^{10}	10^{15}

Table 2. Enhancement of DNA and RNA copy number as a result of different RNA expression levels, after retroviral passage. P= (no. of passages). Numbers are interpreted as relative ratios within a column.

The present invention is able to efficiently create a library of RNA or DNA sequences whether or not they are in low abundance. The kinetics of screening for RNA abundance of a promoter can be appreciated best in the following discussion. For the purposes of this discussion, position effects have been ignored. An equation describing the kinetics of screening for RNA abundancy is:

$$(1)\quad R_{rel\chi}=A\chi/\sum A_{n=\infty}$$

The above equation (1) can be stated in plain English: The relative abundance of an RNA species χ ($[R_{rel\chi}]$within a population of RNA molecules expressed in a single cell or within a population of cells) is equal to the RNA copy number of RNA species χ (A_χ) divided by the sum of the RNA copies of all RNA species present, including χ.

The relative abundance number of any given species changes as the number of passages change, according to the following approximation:

$$(2)\quad R_{\chi py}=D_{\chi p0}R^{p+1}$$

In the simplest of terms, equation two (2) can be expressed as: The abundance of RNA species χ after Y passages ($R_{\chi py}$) is equal to the initial abundance of the DNA for species χ at passage=0 ($D_{\chi p0}$), multiplied by the RNA abundance/DNA copy, raised to the power of the number of passages plus one. Thus, a typical RNA species that starts out as a

single copy of DNA, after zero passages (*i.e.*, in the donor cell) expresses 10 copies of RNA/cell. After one passage it is amplified at the DNA level to a relative ten copies (the same as the RNA abundance at P=0), and at the RNA level to 100 copies (10 copies per DNA copy). The reason for the amplification is that viral packaging and passage is based upon the number of RNA copies present in the donor cell. These calculations can be used to arrive at approximate abundance determinations for any given passage. The actual results of any given experiment, of course, will be biological rather than physical or mathematical. This means that other variables such as RNA efficiency of transmission and longevity, availability of transcription factors, experimental variation, *etc.* also come into play. The underlying purpose of the approximating equations, however, is to illustrate that RNA is amplified in DNA in proportion to the abundance of the template (RNA) within the cell.

The abundance of mRNA in cells can vary continuously from less than a copy per cell to nearly 100,000 copies/cell in actively transcribing, highly-specialized cells such as reticulocytes, the chicken oviduct, the silk moth silk gland, etc. Therefore, the spectrum of RNA abundance from $0\text{-}10^5$/cell is within the biological window of interest. For most practical purposes, such as biotechnological expression of genes in specific cells, only the higher end of this abundance range is desired. Therefore, using a viral selection system, as disclosed in this invention, it may be possible to disregard those species with less than a threshold level, such as <0.1 copies per cell. The selection through virus will lead to the recovery of the more abundant species. Furthermore, because the vector is likely to be the only considered sequence, it may be considered as a proportion of the whole of RNAs expressed in the target cell. The situation is more complex when a large number of permutations and combinations is generated, for example by self-assembling thousands or millions of fragments in a predetermined order using the self-assembly technique of the instant invention. Consider the assembly of allelic variants of four promoter subregions: distal enhancer, proximal enhancer, distal promoter and proximal promoter. If 100 varieties of each of the four groups were amplified and combined using the instant process along with a single vector, 10^8 resultant combinations could occur. However, a sufficient number of molecules to start out a combinatorial screening program might be a million. The problem can be simplified by considering these in groups as follows:

Table 3. Grouped abundance of RNA molecules derived from combinations.

No. of species in group:	RNA abundance:	Total No. RNA molec. at P=0:	RNA at P=1	RNA at P=2	RNA at P=3
9×10^5	1	9×10^5	9×10^5	9×10^5	9×10^5
2×10^5	10	2×10^6	2×10^7	2×10^8	2×10^9
2×10^4	1,00	2×10^6	2×10^8	2×10^{10}	2×10^{12}
1×10^3	1000	1×10^6	1×10^9	2×10^{12}	2×10^{15}
1×10^1	10,000	1×10^5	1×10^9	1×10^{13}	1×10^{17}
1	100,000	1×10^5	1×10^{10}	1×10^{15}	1×10^{20}
Sum Total:		6.6×10^6	1.11×10^{10}	1.01×10^{15}	1×10^{20}

Thus, it follows that in the example population (Table 3) of over a million constructs (equally represented in the DNA), a single construct expressing 10^5 copies of RNA per DNA copy will increase to approximately 99% of the total expressed RNA sequences in two passages. Using similar procedures in combination with drug and/or hormonal stimulation, and after consideration of the possible transcription factor binding sites within the sequence family (Figs. 5 & 6), it is within the intended scope of the invention to select for hormonal or pharmacological controls of transcription such as have been described herein. The factors contributing to the outcome are not only the input constructs, but recombinants and mutants as well. These secondary contributors to molecular diversity will be enhanced if multiple rounds of infections are allowed to occur, as oftentimes the difference between a particular transcription factor being able to bind (or not) may depend upon a single base change. Because viral infection is progressive and competitive, molecular evolution can be used to generate gene constructs *de novo* in the tissue culture dish in short time periods. Advantageously, the use primers to generate amplified fragments with uniquely complementary cohesive ends (i.e., that the ends will preferably only hybridize with the intended 5' and 3' fragments) to ligate three or more fragments as taught in this invention improves the potential for obtaining a diverse library.

Although the examples particularly point out a transcriptional promoter as the product of the process, the skilled artisan can appreciate that a particular selection technique can be applied to other *cis*- and *trans*-acting genetic sequences as well. Although a virus is used to propagate the selective advantage of a preferred embodiment, it can also be appreciated that any selective screen, such as drug selection, cell survival, phenotypic selection, cell sorting, antibody selection, and the like (see Ausuble et al., *supra*) could be

substituted without changing the intended scope of the invention. Likewise, transfection or cell fusion could be used in place of viral infection. Furthermore, substitution of different viruses, retrotransposons, or functional groups are likewise within the intended scope of the invention. The described embodiments are to be considered only as illustrative and not restrictive, and the scope of the invention is indicated by the claims rather than by the narrative description. All references and publications, cited herein, are incorporated by reference into this disclosure.

Like the embodiments detailed above, the method of library production is also conducive to assembly and transfer of genetic material directly into eukaryotic cells, saving the step of propagation in bacteria that is standard in bacteria. An advantage of direct transfer of the libraries of this invention to eukaryotic cells, including the exemplary retroviral vector producer cells, is that certain essential *cis*-acting structural features will be under positive selection (i.e., if they are not present, the molecule will be lost due to its non-functionality). As discussed above, it is often advantageous to eliminate bacterial and plasmid DNA sequences, endotoxin, and other bacterial contaminants by introducing the constructs directly into eukaryotic cells.

In addition to providing a method for constructing complex DNA molecules efficiently (as in the examples of three piece and six piece constructs), the methods of this invention permit the assembly of constructs that are larger than those conventionally propagated in *E. coli*. Examples of these types of vectors include adenovirus vectors, herpes simplex vectors and artificial minichromosomes. In order to insert genes into such vectors that are too large for conventional molecular cloning procedures, in the past it was often necessary to resort to *in vivo* recombination, wherein the genes of interest are cloned into a suitable vector and the flanking homologous regions are used to target the foreign genes to a homologous site within the larger viral or minichromosome vector. However, the methods of this invention permit PCR fragments of any size (up to the limits of PCR capability, 20-30 kb per fragment) to be joined together. Thus, it is feasible to precisely construct adenovirus vectors by amplifying larger sequences, and combining them by ligation. For example, several sections of adenovirus (5-10 kb each) can be ligated using the methods of this invention, up to for example, about 37 kb, and then transformed directly into human cells. Only the correctly recombined vectors are capable of replicating. Hence, the DNA is autoselecting. A similar procedure is used for generating herpes virus vectors, which are

approximately 150 kb. The precision of the methods of this invention permit non-essential viral genes to be more easily eliminated from the construct. After transfection into appropriate cells, the DNA replicates and virus particles are formed.

Some special considerations apply to larger vectors, however. First, it is desirable to use enzymes that do not cut within the large DNA fragments. To prevent excessive fragmentation of the DNA by internal sites, it is desirable to use enzymes that cut rarely or infrequently, such as CpG-containing enzymes recognizing six bases, or enzymes such as *Sap*1, recognizing seven bases and digesting a three bp overhang (thus permitting up to 32 fragments to be joined in order). It is also desirable to avoid shearing the DNA once large segments have been joined by ligation. One method of avoiding shear is to add the transfection agent, such as Superfect™ reagent (dendrimers, Qiagen) or Lipofectamine™ (liposomes, Life Technologies, Gaithersburg, MD) directly to the ligation reaction, and then add the cells to be transfected to the mixture. This, or a similar method avoids the need to physically move the ligated DNA, and thus prevents shearing. Another method is to add a DNA condensing reagent (dendrimers, polycations [such as polyethyleneamine] histones or liposomes) directly to the DNA ligation reaction, and then move the DNA by pipette after it has condensed (thus reducing shearing of the DNA). Once inside the cell, viral DNA can replicate (as in the examples of partially replication-competent adenovirus and herpes simplex virus vectors).

Artificial minichromosomes have been under development for years. True artificial chromosomes require a centromere, at least one origin of DNA replication, and in the case of linear molecules, telomeric repeats at the chromosomal termini. In addition, to be very effective it is desirable to have a selectable marker gene, one or more therapeutic genes, and/or reporter genes.

In reality, the use of minichromosomes has been delayed by the inability to effectively manipulate the larger DNA molecules *in vitro*. Yeast and bacterial artificial chromosomes have been used with little success in mammals, and the addition of telomeres to the ends of linear chromosomes is also a special problem, as there is no prokaryotic host that can tolerate large linear DNA. The methods of this invention offers the opportunity to assemble human or mammalian minichromosomes *in vitro*, by using large segments (10-30 kb) of synthetic, gene-amplified DNA as ligation starting materials. For example, up to 32 *Sap*1 fragments (up to 30 kb each, containing the essential *cis*- and *trans*-acting sequences),

or 512 shorter *Hga*1 fragments can be combined using these methods. As with the other examples, several enzymes suitable for this invention (e.g., such as class IIS enzymes) can be combined (possibly with different termini lengths) to simplify the task. The methods of this invention also facilitate construction of telomeric repeats, because the constructs of this invention do not need to be circular. Thus, the methods of this invention can be used to make telomeres of any length, by adding additional segments onto the ends of molecules. One way to do this is using self assembling genes that employ a repeating overhang sequence (self-complementary molecule, such as AG-3' at one end, and CT-3' at the other end), permitting the telomeres to be lengthened to the extent desired by adding the required molar excess of the telomeric repeat-containing fragment. This technique gives the investigator some control over the relative length of the telomeres, although the self-complementarity indicates that many repeats will be lost due to self-ligation. This can be alleviated by using higher starting concentrations of DNA to favor inter-molecular ligations over intra-molecular ligations (e.g., >20 μg/ml starting concentration of DNA).

A two fold molar excess of telomeric fragments gives approximately twice the average length of telomere as a strictly 1:1 molar ratio of all fragments. By using a higher molar ratio of shorter telomeric repeats it is possible to give greater uniformity to the overall length of the molecules, which will vary from one terminus to the other. Thus, in addition to providing a way to build large molecules with precision, the methods of this invention provides for a way to control the telomere length (or potential life-span) of the artificial chromosome. To prevent damage during handling, the minichromosome DNA can be condensed with polycations, adenovirus particles, dendrimers, histones, or liposomes prior to transfection, similar to larger viral vectors.

The methods of this invention can be used to create recombinant virus. One example of this is an adenovirus vector self-assembling gene system. This system can include three parts: 1) vector: 2) helper virus; and 3) helper cells. The vector part is a self-assembling fragment set of at least three fragments comprising the essential cis-acting sequences (left and right inverted terminal repeats, which are the 103 bp at both ends of the genome that are required for replication [ITRs] and packaging sequences [Y, base pairs 194-358) and central 'baggage' area, comprising one or more self-assembling fragments including therapeutic genes, marker genes, and reporter genes. The baggage area is thus flanked by the cis-acting sequences in the vector. Because the synthetic oligonucleotide sequences

comprising the 5' and 3' termini of the helper virus are not phosphorylated, they will not ligate together creating multimers. Thus, the Ad5 vector region will assemble only into monomers. The helper virus part comprises all Ad5 trans-acting genes except for the ElA and ElB genes. The helper virus part has no cis-acting sequences, and it is amplified in several sections. In this preferred embodiment, the virus is amplified using primers that exclude the ITRs, packaging region and E1A&B genes. The helper virus is digested by *Sap*1 digestion, creating seven uniquely terminated fragments comprising the trans-acting viral genome, with dephosphorylated, blunt 5' and 3' ends on the terminating fragments. The primers are designed so as to amplify the internal virus sequences without changing them, except for the 5' and 3' ends of the virus. The PCR-amplified fragments are digested with *Sap*1 and are religated in their natural order after gel isolation and Qiagen column purification. The 5' end of the helper virus genome starts at 3.2 kb (in the E1A gene) so as not to overlap the vector sequences, which could otherwise cause replication competent adenovirus (RCA). Because the. 5' and 3' ends of the helper virus do not contain Sap1 sites, they remain intact after digestion with *Sap*1. Because the synthetic oligonucleotide sequences comprising the 5' and 3' termini of the helper virus are not phosphorylated, they will not ligate. Thus, the Ad5 helper virus genome assembles only into preferred monomers during ligation.

In a preferred embodiment, non-essential genes are deleted from the Ad5 genome by means of the method of self-assembling genes. In another preferred embodiment, the helper virus genome is approximately 30 kb after deletion of ElA, E1B and E3 gene sequences from the helper virus, and it is amplified as a single long fragment using the eLONGase Amplification System (Life Technologies or a similar strategy for creating long PCR fragments with high fidelity). It is not of great importance that occasional PCR errors may occur, because multiple copies of the Ad5 helper virus are transfected into target cells, thus providing trans-complementation. The helper cells are preferably 293 cells, a human kidney cell line expressing ElA and ElB genes (ATCC). The vector part and the helper virus part are combined in equimolar ratios after ligation has been performed separately on each fragment set. The Superfect protocol (Qiagen) is used to transfect the vector part and the he.lper part into the helper cells. The helper cells lyse, releasing high-titer adenovirus particles that are capable of infecting a variety of human cells. The resulting defective virus is incapable of forming RCA, and it transmits up to 34 kb of foreign genes in the baggage area. Unlike conventional Ad5 vectors that require separate constructs for E. coli propagation of

insert genes, and recombination in vivo, the present vectors are relatively easy to make and provide a precise, safe alternative to first generation and second generation adenovirus vectors.

Exemplary methods for producing self-assembling vectors and genes are provided below. Further, the Examples provide methods for producing libraries of nucleic acid sequences using the methods of this invention. A number of nucleic acid sequences identified using the methods of this invention are described. The examples provided below are exemplary and not limiting. All references and publications provided herein are incorporated by reference into this disclosure.

Example 1
Three-Piece Gene Self-Assembly with 100% efficiency

Using 6 primers (SEQ ID NOS:24 and 63-67), three PCR fragments were amplified from templates VLMG (SEQ ID NO:22) and VLBPGN (SEQ ID NO: 1). PCR reactions were carried out using the hot start technique, according to the manufacturer's instructions (Perkin Elmer) using *Pfu* DNA polymerase (Stratagene). To amplify specific portions of the above templates, each primer contained a class IIS enzyme site capable of digesting a unique overhanging end that was complementary to only one other terminus in the subsequent ligation. The class IIS enzymes used were *Bpm*1 and *Eco* 57I (the latter was used to copy a fragment that contained an internal *Bpm*1 site). The reactions were carried out as follows: 1) the lower reaction was assembled according to the protocol for PCR Gems (Perkin Elmer); 2) the lower reaction was heated to 80°C, 5 min, then cooled to 4°C for 5 min; 3) the upper reaction was prepared according to PCR Gems protocol and was added to the lower reaction (separated by cooled wax). The primer concentration was 0.3 μM (final). The dNTP concentration was 200μM (final). 5 Units of *Pfu* polymerase was used. All fragments were amplified using the following conditions: 96°C, 45 sec; (then followed by 30 cycles of the following) 96°C 45 sec, 52°C 45 sec, 72°C, 6 min; then followed by a single incubation at 72°C for 10 min; then hold at 4°C. All fragments were successfully amplified. The PCR fragments were purified using the Qiaquick PCR purification protocol (Qiagen). The fragments were digested with an excess of the appropriate restriction enzyme (*Bpm*1 or *Eco*57I). The digested fragments were run on a 1% agarose gel and were excised using minimal irradiation from a hand-held 365 nm ultraviolet light. The fragments were purified

using the Qiagen Qiaquick Gel Purification Protocol. The fragments were ligated at an equimolar ratio at a concentration of >20μg/ml with T4 DNA ligase (Boehringer Mannheim) overnight at 4°C. Competent *E. coli* SCS110 cells (Stratagene) were transformed with the ligated DNA. Eight colonies were characterized by restriction enzyme analysis, and all eight contained the correct order and orientation of the three fragments. The experiment was repeated independently by another investigator, and the same result was obtained (8/8=100%). Thus, the procedure resulted in a high percentage of correctly assembled vectors.

This three-piece vector was VLΔBP. The deletion extended from the distal enhancer region to the TATA box near the start of transcription. The deletion region was a pair of *Bpm*1 sites that permitted U3 sequences to be cloned into the insert.

One validated *E. coli* clone of VLΔBP was transfected into retroviral helper cells. After 48 h, the vector was transduced into amphotropic helper cells. After selection for two weeks with the drug G418, drug resistant colonies were grown up in a mass culture and the vector was transduced from the amphotropic helper cells into a human HT1080 cell line (ATCC, Rockville, MD). Surprisingly, even with a large deletion in the LTR promoter, the basal TATA box-containing VLΔBP was transmitted as a retrovector and was permanently inserted into the human cell line, thus establishing the validity of the self-assembly technique for the construction of functional eukaryotic vectors.

Example 2
Production of a Six Piece Self-Assembling Expression Vector

Due to the high efficiency of the gene self assembly process for the three piece assembly, a complex vector containing six fragments was constructed. The results here were extended to determine whether such a self-assembled vector would also have biological activity in human cells without being cloned and grown in a prokaryotic cell.

Six fragments were individually constructed by PCR using three different templates and twelve primers (as illustrated in Fig.8). The primers used three different class IIS enzymes. The enzymes were chosen so as to give 2 base pair, 3'-overhanging ends. Three enzymes were used in order to avoid the use of enzymes that had additional sites internal to the fragments being amplified. Thus, *Bpm*1 was used unless there was an internal *Bpm*1 site. If such a site existed, *Eco*57I was used. If there was also an internal *Eco*57I site, then *Bsr*D1

was used. However, it is alternatively possible to use an enzyme such as *Eam*11041, where the *Eam*11041 sites in the primers are unmethylated (therefore susceptible to digestion by the enzyme), and wherein the ^{m5}dCTP analog of dCTP is used in the PCR reaction, methylating all internal sites (and protecting them from digestion by *Eam*11041), as suggested by Padgett and Sorge, 1996, *supra*, and incorporated herein by reference.

Using 12 primers, 6 fragments were amplified from 3 templates: pBK-CMV (SEQ ID NO:26) , pVLMB (SEQ ID NO:23) and pVLOVhGH-900 (SEQ ID NO:21). Fragment 1 was amplified from pBK-CMV using primers 1 and 2 (SEQ ID NOS:31 and 32). Fragment 2 was amplified from pVLMB using primers 3 and 4 (SEQ ID NOS:33 and 34). Fragment 3 was amplified from pVLOVhGH-900 using primers 5 and 6 (SEQ ID NOS:35 and 36). Fragment 4 was amplified from pVLMB using primers 7 and 8 (SEQ ID NOS:37 and 38). Fragment 5 was amplified from pVLMB using primers 9 and 10 (SEQ ID NOS:39 and 40). Fragment 6 was amplified from pVLMB using primers 11 and 12 (SEQ ID NOS:41 and 42). PCR reactions were carried out using the hot start technique, according to the manufacturer's instructions (Perkin Elmer Ampliwax PCR GEMS 100). The lower reaction was heated to 80 ° C for 5 min, then cooled to 20 °C for 5 min. The upper reaction was prepared according to PCR gems protocol and was added to the lower reaction (separated by cooled wax). The primer concentration was 0.3 micromolar (final). The dNTP concentration was 200 μM (final). 5 U of *Pfu* polymerase (Stratagene) was used per reaction. 100 ng of template was used for each reaction 14 rounds of PCR amplification were used to reduce mutagenesis of the templates. The PCR cycling protocol was 96 °C 45 sec; then two cycles of (96°C 45 sec, 52°C 45 sec, 72°C 6 min); then 12 cycles of (96°C 45 sec, 58°C 45 sec, 72°C 6 min) followed by a 72° C soak for 10 min, then to 4°C hold.

The six PCR fragments were designed to self-assemble into a retro-vector after digestion with the correct class IIS restriction enzyme (Fig. 8). After transfection into retroviral helper cells, the vector DNA is transcribed as RNA by means of the cytomegalovirus immediate early promoter (fragment 1). This promoter replaces the retroviral or VL30 LTR in this vector. The RNA transcript region begins with the R and U5 regions of the Moloney murine leukemia virus (MoMLV) LTR, the viral packaging signals (Ψ) region of MoMLV, the packaging enhancer (Ψ+) region of mouse VL30 and the IRES region of EMCV fragment 2. Fragment 3 consists of the human growth hormone (hGH) cDNA sequence. Fragment 4 consists of the SV40 virus early region promoter driving

expression of the neomycin phosphotransferase (neo) gene. Fragment five consists of the (+)-strand primer binding site of the MoMLV LTR, the U3 region of the MoMLV LTR, the repeat (or R) region, and a portion of the U5 region. Fragment 6 consists of the PBR322 plasmid origin of replication.

Fragment 1: CMV early region promoter

Template: pBK-CMV plasmid DNA (Stratagene, LaJolla, CA) *Bpm*1 (SEQ ID NO:26)

PCR primer 1 (SEQ ID NO:31)

GACTAACCTTGATTCCA**CTGGAG**CCGTATTACCGCCATGCATTAGTTATTAATAG

PCR primer 2 (SEQ ID NO:32)

GACTAACCTTGATTCCA**CTGGAG**TAATTGCGGCTAGCGGATCTGACG

Fragment 2: R-U5-Psi-Psi(+)-IRES *Bpm*1

Template: pVLMB plasmid DNA (SEQ ID NO:23)

PCR primer 3: SEQ ID NO:33

GACTAACCTTGATTCCA**CTGGAG**ACACTTGACCTCTACCGCGCCAGTCCTCCGAT TGACTGAGTCG

PCR primer 4: SEQ ID NO:34

GACTAACCTTGATTCCA**CTGGAG**GGATCCGCGCCCATGATTATTATCG

Fragment 3: human growth hormone (hGH) *Bsr* DI

Template: pVLCNOVhGH plasmid DNA (SEQ ID NO:21)

PCR primer 5: SEQ ID NO:35

GACTAACCTTGATTCCA**GCAATG**TCGGTTAGCTTGTTTCTTTACTGTTTGTC

PCR primer 6: SEQ ID NO:36

GACTAACCTTGATTCCA**GCAATG**TTAGGACAAGGCTGGTGGGCACTGG

Fragment 4: SV40 early promoter-neomycin phosphotransferase

Template: VLMB plasmid (SEQ ID NO:23)

PCR primer 7: SEQ ID NO:37

GACTAACCTTGATTCCA**CTGGAG**GGTCGACCCTGTGGAATGTGTGTCAG

PCR primer 8: SEQ ID NO:38

GACTAACCTTGATTCCA**CTGGAG**AATCTCGTGATGGCAGGTTGGGCGT

Fragment 5: MLV(+)PBS-U3-R-U5

Template: VLMB plasmid (SEQ ID NO:23)

PCR primer 9: SEQ ID NO:39

GACTAACCTTGATTCCA**CTGAAG**AGATTTTATTTAGTCTCCAGAAAAAGGGGGG

PCR primer 10: SEQ ID NO:40

GACTAACCTTGATTCCA**CTGAAG**CCCCCAAATGAAAGACCCCCGCTGACG

Fragment 6: PBR322 origin of replication

Template: VLMB plasmid (SEQ ID NO:23)

PCR primer 11: SEQ ID NO:41

GACTAACCTTGATTCCA**CTGGAG**CCGGGACGGAATTCGTAATCTGCTGC

PCR primer 12: SEQ ID NO:42

GACTAACCTTGATTCCA**CTGGAG**TTCTCGAGGCGGCGCATCTCGGCG

Procedure: The twelve primers were prepared by the following procedure: 1) oligonucleotides were synthesized with trityls off. After deprotection and lyophilization, the samples were resuspended in 5 microliters deionized formamide and loaded onto a polyacrylamide gel (12% polyacrylamide, 250V). The samples were excised under short wave UV irradiation and eluted overnight in 600 microliters of sample elution buffer (0.5 M ammonium acetate, 10 mM Mg acetate, 1 mM EDTA, 0.1% SDS). The contents were loaded onto a BioRad Chromatography column (Cat. # 732-6008) and centrifuged into an Eppendorf tube at low speed (2000 RPM, 5 min). After washing the column with 500 microliters TE buffer (10 mM Tris, 1 mM EDTA), pH 8.0 and recentrifugation (2000 RPM, 5 min), the pooled eluate was ethanol precipitated, washed with 100% ethanol, resuspended in TE buffer and quantitated by spectrophotometry of a small sample, which was then discarded.

Fragments were cleaned using the Qiaquick PCR cleanup procedure. The fragments were digested with their respective class IIS restriction enzyme. The digested fragments were run on 1% agarose gels, and the fragments were excised and cleaned using the Qiaquick gel cleanup procedure. Fragments were combined in an equimolar mixture and

ligated overnight at 4° C with T4 ligase and ATP. An analytical gel was run with the ligated DNA, as well as with controls including unligated fragments and ligated fragments with a single fragment missing. As opposed to the controls, the complete ligation included bands equivalent to the full-length supercoiled monomer (refered to as GENSA 981, SEQ ID NO:29), as well as bands possibly representing multimers (up to six bands were observed).

In order to assess the efficiency of the method, eleven nanograms of DNA were transfected into SCS1 supercompetent cells. Thirteen kanamycin resistant colonies were harvested, and plasmid DNA preps indicated 10 out of thirteen that appeared to be the correct length. All ten gave the expected bands when digested with *Pst*1, *Sna*B1, and *Bam* HI. 1.35 μg of the ligated DNA was purified by phenol-chloroform-isoamyl alcohol extraction, followed by two extractions with chloroform-isoamyl alcohol, and was precipitated in ethanol. The DNA was washed in 70% ethanol and re-suspended in 50 μl of sterile phosphate buffered saline (for transfection). The DNA was transfected (using the Qiagen Superfect protocol) into HTam1 (amphotropic human helper cells). 24 h after transfection, the target cells were washed and fresh culture media was added. 48 h after transfection, the supernatant from the vector producer cells was filtered (0.45 μm, Nalgene) and transferred to PG13 helper cells (ATCC) and HT1080 human fibrosarcoma cells. This procedure was repeated after 72 h. 48 h after transduction, recipient cells were started on G418 drug selection (500 μg/ml). The appearance of G418 drug-resistant colonies on transduced PG13 and HT 1080 cells after 6 days of selection indicated successful transmission via retrovirus particles. The transfect HTam cells were also selected with G418. After six days of drug treatment, 45 colonies of resistant cells were counted. Thus, the six fragment gene assembly was effectively transmitted and expressed as either a DNA (transfection) vector or a retro-vector.

Example 3
Design and Construction of Single LTR Vectors

Background: In order to manipulate the interior of the VL30 LTR sequences using a promoter rescue technique, single LTR vectors were constructed. The mouse VL30 element NVL-3 was used as the starting material as it is constitutively and abundantly expressed in most mouse tissues. Single LTR vectors are circular and behave as if they contained two LTRs. Thus, in these vectors RNA transcription begins at the start of the R region (see Fig.

3B), and continues through the polyadenylation site after completing the second round of transcription of the R sequences (Fig. 3A). In previous studies, these vectors were expressed transiently in vector producer cells and the DNA did not integrate into cell DNA as a standard two LTR vector. Therefore, the vectors were usually passed to a second complementation helper cell line via retroviral transduction of the vector RNA transcribed in the first helper cell. This process resulted in the vector regenerating a correct (two LTR) structure upon integration into the recipient cell DNA.

Experimental method: The plasmid pNVL-3 (SEQ ID NO:25, kindly provided by Dr. J. Nortonm Manchester, UK), containing a complete copy of the NVL-3 (mouse VL30) genome (Adams *et al*, 1989), was digested with *Xho*1 (which cuts in the LTRs), releasing the 4.27 kb VL30 genome with one copy of the LTR. This fragment was circularized using T4 DNA ligase and ATP. The circular DNA was linearized by digestion with *Sna*BI, 187 bp from the 3'-LTR. A 2.3 kb fragment containing the SV40 virus early region promoter and the aminoglycoside phosphotransferase (*neo*) gene, together with the PBR322 plasmid origin of replication, was excised from the BAG retrovirus vector (Price *et al., Proc. Natl. Acad. Sci.* 84:156-160, 1987, kindly provided by C. Cepko, Cambridge, MA). BAG is also obtainable in a retrovirus helper cell line from American Type Culture Collection (ATCC), Rockville, MD by digestion with *Xho*1 and *Bam*HI. This fragment was blunted with T4 DNA polymerase and dephosphorylated with calf intestinal alkaline phosphatase (CIP). The fragment was then ligated to the linearized *Sna*BI fragment of NVL-3. The resulting plasmid (containing a circularly permuted NVL-3 genome with the SV-*neo-ori* region) was designated VLSNO2 (SEQ ID NO:30).

In order to facilitate the switching of LTR sequences by means of the class IIS enzyme *Bpm*1, VLSNO2 was digested with *Bpm*1 (six sites). The region containing four *Bpm*1 sites was removed and replaced with a 19 bp linker (SEQ ID NOS: 1 and 52, see below), 921 bp beyond the LTR. The linker contained *Sna* BI, *Cla*1 and *Bam* HI cloning sites.

Linker (top strand): 5'-TACGTATCGATGGATCCGA-3' (SEQ ID NO:51)

Linker (bottom strand): 5'-GGATCCATCGATACGTAAG-3' (SEQ ID NO:52)

The remaining two of the *Bpm*1 sites had complementary ends, which permitted their ligation and resulted in eradication of all *Bpm*1 sites within the resulting vector VLSNO3 (SEQ ID NO:20).

In order to facilitate reporter/therapeutic gene function, a 3.7 kb fragment containing the internal ribosome entry site (IRES) from encephalocyocarditis virus, together with the β-galactosidase reporter gene, was excised from the plasmid pVLSAIBAG (kindly provided by Mr. James Grunkemeyer, Omaha, NE) by means of a partial digestion of the plasmid with *Bam* HI. This region was inserted into the *Bam* HI site of VLSNO3, resulting in the vector VLSNOSIB (SEQ ID NO:14).

A second reporter construct, pVLSNOG (5774 bp, SEQ ID NO:19) contained the green fluorescent protein (GFP, Clontech, Palo Alto, CA) gene was constructed by inserting a *Bgl*2-*Bcl*1 fragment (800 bp) from plasmid pGFP-N1. This sequence, containing the GFP gene, was treated with mung bean exonuclease and inserted into the unique *Sna* B1 site of pVLSNO3.

In order to enhance GFP fluorescence from the reporter plasmid pVLSNOG, the serine-65 codon in the GFP gene was mutated into threonine by a site-directed mutagenesis procedure with the Transformer™ Site-Directed Mutagenesis kit from Clontech. A *Bpm*1 site in the GFP gene (threonine-9) was mutated at the same time without changing the amino acid (ACT to ACA). The resulting plasmid was pVLSNOGM (SEQ ID NO:18).

An *Nco*1-*Xho*1 fragment (585 bp) from plasmid pG1IL2EN (kindly provided by Dr. Steven Rosenberg, Bethesda, MD), containing the internal ribosome entry site (IRES) from encephalomyocarditis virus (EMCV) was inserted into the *Apa*1 site upstream of the GFP gene in pVLSNOGM, resulting in pVLSNOGMI (SEQ ID NO:17). Both insert and plasmid fragments were blunted with mung bean exonuclease. One variant version of pVLSNOGMI with an IRES tandem dimer was also constructed and designated pVLSNOGMI2 (SEQ ID NO:16).

Oligonucleotides (SEQ ID NO:53 and 54) containing a splice acceptor (SA) of AKV virus (in bold) was inserted into pVLSNOGMI at the unique *Sac* 2 site just before the IRES, resulting in pVLSNOGMIS (SEQ ID NO:15).

Oligo: (SEQ ID NO:53)

5'-GGCCGC**TAACTAATAGCCCATTCTCCAAGG**TACGTAGC-3'

3'-CGCCGGC**GATTGATTATCGGGTAAGAGGTTCCATGCAT**-5'

(SEQ ID NO:54, bottom Oligo)

Recovery of LTR promoter sequences from mouse CD4+ T-helper cells

In order to facilitate the recovery of VL30 promoter sequences expressed in mouse T-helper cells, a mouse CD4+ T-helper cell cDNA library (Stratagene, San Diego, CA, Catalog # 937311) was screened by plaque hybridization. Approximately 2 x 10^4 bacteriophage λ-ZAP clones were plated on a lawn of *E. coli* cells according to the manufacturer's instructions. Two nylon filters were sequentially layered onto the lawn of *E. coli* cells and bacteriophage. The filters were hybridized to a ^{32}P-labelled (Prime-It RmT Random Primer Labeling Kit, Stratagene), 4.2 kb internal *Xho*1 fragment of NVL-3 (containing the NVL-3 genome). 55 plaques (or approximately 0.3% of the total phage) reacted positively on both filters. 18 VL30 cDNA sequences were cloned from the plate, which was used to identify U3 promoters that are actively expressed in the RNA of mouse T-cells. Five of the 18 clones contained intact U3 sequences, representing four of one molecular species, named TH1 (SEQ ID NO: 2) and one of another species, named TH2 (SEQ ID NO: 3) also provided in Fig. 5. TH1 contained approximately 120 bp more DNA than did TH2. Because TH1 was more abundant (4 out of 5 clones), the additional sequences in the enhancer region were implicated to be a possible reason for the stronger expression in mouse T cells. Examination of the known and putative transcription factor binding sites in the VL30 LTR (Hodgson, 1996, chapter 4, Fig. 4.2 *supra*) revealed several interesting features of TH1 and TH2. First, the extra sequences of TH1 that were missing in TH2 included an extra copy of the enhancer repeat region as well as a potential retinoid (RAR/RXR) binding site. Several transcription factor binding sites in the enhancer repeat region that differed between the two elements included: a cyclic 3'-5'AMP response element (VLCRE, a potential CREB/jun binding site), a serum response element (SRE), and a potential NF1/IL6 binding site (although there were additional sites for these factors in other enhancer repeats). These factors could possibly explain why VLTH1 appeared to be expressed at higher levels, both in the source cells and into transduced cells. Together, the VL30 sequences represented 0.3% of the mRNA expressed in the T cells, and TH1 appeared to be most abundant VL30.

Sequencing Primers:

(SK, SEQ ID NO:49) 5'-CGCTCTAGAACTAGTGGATC (20 mers, Tm 60°C).

(T7, SEQ ID NO:50) 5'-GTAATACGACTCACTATAGGG (21 mers, Tm 60°C).

Seamless Rescue of T cell promoters using class IIS restriction enzymes

Two sets of primers containing offset *Bpm*1 restriction sites were designed and synthesized. One set was for amplification of the plasmid sequences, and another was for the amplification of the inserts.

Insert Primers: (Bpm1 site bold)

ITA (43 mer, Tm: 67.2 °C, SEQ ID NO:45)

CGATCCA**CTGGAG**CTCGGAGCCCACCCCCTCCCATCTAGAGGT

ITB (43 mers, Tm: 66.3 °C, SEQ ID NO:46)

CGTCCTC**CTGGAG**AGCACAGGGTAGAGGAGTCTCGACGGTCAG

Vector primers: (Bpm1 site bold)

VLA (43 mers, Tm: 68.2 °C, SEQ ID NO:47)

CGCAACC**CTGGAG**ACCTCTAGATGGGAGGGGGTGGGCTCCGAG

VLB (43 mers, Tm: 66.3 °C, SEQ ID NO:48)

GCAGGAC**CTGGAG**CTGACCGTCGAGACTCCTCTACCCTGTGCT

To amplify vector sequences more efficiently, vector templates were shortened by deleting marker genes from vectors. pVLSNOSIB (SEQ ID NO:14) was cut with *Kpn* 1 and a 4201 bp fragment containing β-gal gene was removed. The remaining vector has 3923 bp.

The U3-promoter inserts (357 bp for TH1 and 240 bp for TH2) were PCR-amplified from TH1 and TH2 promoters with primers ITA and ITB. The vector cassettes (~4.2 kb for pVLSNOSIB and ~3.7 kb for pVLSNOGMIS) were PCR-amplified from the shortened vector templates using primers VLA and VLB, (*supra*). The PCR-amplification was done with high-fidelity *Pfu* DNA polymerase from Stratagene (La Jolla, CA). The amplified products were gel-purified (1% agarose gel). The inserts were then cut with *Bpm* 1 to produce complementary ends. The vector cassette products were phosphorylated with

PNK, then circularized with T4 ligase, and transformed into SCS 110 cells. Recovered plasmids were then digested with *Bpm* 1 and treated with CIP to produce complementary ends. *Bpm* 1 treated inserts and vector cassettes were ligated, and T-cell tissue-specific VL 30 vectors VLTH1 and VLTH2 were produced. The marker β-gal gene and GFP gene were put back into those vectors at the original unique sites *Kpn* 1 and *Sal* 1 respectively.

Transmission and expression of single LTR vectors and T cell U3 sequences

Vector DNA constructs were transfected into GP+E86 retroviral helper cells (Markowitz et al, 1988, *supra*) using the Lipofectamine protocol (Life Technologies, Gaithersburg, MD). The culture media from these cells (supernatant), containing defective transducing particles (72 h post-transfection), was transmitted to PA317 (Miller, US Patent, cited *supra*) amphotropic helper cells, using Lipofectamine to enhance transduction efficiency (Hodgson *et al.*, 1996. Synthetic Retrotransposon Vectors and Gene Targeting pp. 3-14, in : Felgner et al., eds. *Artificial Self-Assembling Systems for Gene Delivery*. American Chemical Soc. Books, Washington, D.C.). A similar procedure was used to transmit VLTH1 and VLTH2 to the PG13 helper cell line (Miller *et al.*, 1991. *J. Virol.* 65:2220-2224). 24 h post-transfection, the recipient cells were selected with the drug G418 (500μg/ml, 2 weeks) to enrich for stably transduced cell populations.

All of the single LTR vectors, including VLTH1 and VLTH2 were transmitted by this method, indicating that single LTR vectors can be used for promoter switching and yet revert to dual LTR vectors after a single passage. Vectors VLSNO2, VLSNO3, and VLSNOSIB were then titered on NIH 3T3 cells (using the PA317 vector producer cell lines). VLTH1 and VLTH2 vectors were titered on human HT1080 cells (PG13 cell lines). Surprisingly, all of the single LTR vectors were transmitted effectively. However the titers of stably transduced TH1 and TH2 cell lines were 5.5×10^2-1.1×10^3 TU/ml, compared to 0.4-3.0×10^4 TU/ml for the VLSNO2, VLSNO3 and VLSNOSIB cell lines. Thus, switching from the NVL-3 transcriptional promoter (originally isolated from NIH 3T3 fibroblast cells) to VL30 promoters derived from T helper cells, appeared to have a negative effect on RNA expression in fibroblast cells, as determined by the transmissibility of the RNA.

In order to study the usefulness of rescued promoters as DNA transfection vectors (as opposed to retro-vectors), VLSNOSIB, VLTH1 and VLTH2 were also transfected into a number of cell lines (using Lipofectamine), including NIH 3T3, PA317, GP+E86,

PG13, HT1080, SW480 and HeLa (available from ATCC). RNA expression in these cell lines is shown in Table 4, wherein gene expression from the LTR promoter (as determined by β-gal staining) is normalized to VLSNOSIB (100).

Cell line:	NIH 3T3	PA317	GP+E86	PG13	HT1080	SW480	HeLa
Vector:							
VLSNOSIB	100	100	100	100	100	100	100
VLTH1	39.3	18.7	0.1	21	25.5	156	156
VLTH2	28.6	7.1	5.5	11.5	46.8	82	156

Table 4. Transient expression of a β-gal marker gene by three VL30 promoters: NVL-3 (VLSNOSIB), VLTH1 and VLTH2. Cells were transfected using the Lipofectamine procedure. Total blue cells were counted from each well in 6-well plates, and the number of blue cells from VLSNOSIB was normalized to 100%.

The expression of both the VLTH1 and VLTH2 promoters was significantly reduced compared to VLSNOSIB in cell lines of fibroblastic origin, whereas in SW480 colorectal cancer cells and HeLa cells, it was comparable to or better than VLSNOSIB (the NVL-3 promoter). However, VLSNOSIB was expressed poorly in the non-fibroblastic cell lines, so a direct comparison was difficult to interpret. Unfortunately, the human T cell lines (Jurkat and MOLT4 [obtained from ATCC]) were not transfected by Lipofectamine, and they were poorly transduced by VLTH1 and VLTH2 retro-vectors. In the Jurkat and MOLT4 cells transduced with VLTH1 and VLTH2, only a small percentage (1-10%) of cells that were stably transduced by the vectors stained positively for β-gal expression. However, the marker gene (neo) continued to be expressed from an internal promoter, as evidenced by drug selection.

Taken together, the results demonstrated: 1) the ability of the promoter rescue technique to seamlessly capture functional transcriptional promoters from specialized cells; 2) the ability of single LTR vectors to introduce the rescued promoters into standard transducing vectors; 3) the ability of the rescued promoters to be expressed at differing levels in several different cell types, including T cells; and 4) screening and selection established the efficacy, or lack thereof, of individual promoter sequences.

Although the general method of promoter rescue was demonstrated by the foregoing experiments, the titers obtained from the sLTR VL30 vectors may not be useful where selection systems are not available.

Additional experimentation led to the development of a chimeric packaging signal, combining the essential packaging signal from Moloney murine leukemia virus (Ψ), and the enhanced packaging signal (Ψ+) from a mouse VL30 element. A vector embodiment of this packaging system is VLMB (SEQ ID NO:23). One advantage of the chimeric packaging system was the elimination of retroviral *gag* gene sequences that were present in previous high-titer MLV-based vectors (viral *gag* sequences contribute to the generation of replication competent retrovirus outbreaks). The titers of VLMB-based vectors ranged from approximately 1 x 10^5 to 4 x 10^6 TU/ml.

Construction of a cloning vector for promoter rescue

Using pVLSNOGMIS as a template, and primers (SEQ ID NOS:28 and 68), a 6.4 kb plasmid fragment was PCR amplified (Using Hot Start Ampliwax PCR Gems 100, Perkin Elmer). 30 cycles of PCR were performed by following the manufacturer's instructions, with the following input conditions: lower reaction, 80° C, 5 min., then add upper reaction and template, 96° C, 1 min. Each reaction vial contained 50 ng template, 0.5 μM each primer, 200 μM dNTPs and 5U (2μl) *Pfu* polymerase (Stratagene, LaJolla, CA). 30 repeating cycles of: 96° C, 45° sec; 50° C, 45 sec; 75 C, 1 min. A final incubation of 75° C, 10 min, then hold at 4° C. After amplification, the reactions were purified using Qiaquick PCR Purification Kits (Qiagen). The PCR products were digested with *Pac*1, heat inactivated (65° C, 20 min) and ligated together using T4 DNA ligase (overnight at 4° C in a 5 μl vol). The ligated DNA was transfected into SCS110 *E. coli* cells (Stratagene) with kanamycin (50 μg/ml) antibiotic added to the agar plates. The cells were *dcm*$^-$, *dam*$^-$ (to prevent methylation of *Bpm*1 sites). The resulting plasmid, pVLBPGN (SEQ ID NO:1, Figs 2 &3) has a deletion in the U3 region of the LTR. A linker containing a central *Pac*1 site flanked by two outwardly-digesting *Bpm*1 sites occupies the site of the deleted U3 sequences. The *Bpm*1 sites enable the plasmid to be digested with *Bpm*1, resulting in two 2 bp 3'-overhanging ends that are complementary to the U3-derived RT-PCR inserts described below. The digested plasmid was purified free from the intervening linker sequences from an agarose gel after digestion with *Bpm*1, using the Qiaquick gel purification kit (Qiagen).

Procedure for amplification of liver U3 promoter region

Purified mouse liver total tissue RNA was purchased from Ambion, Inc., (Austin, TX). Total liver RNA was treated with RQ1 Rnase-free (Promega, Madison, WI). Using Perkin Elmer Gene Amp thermostable rTth reverse transcriptase RNA PCR kit (P/N N808-0069), the following conditions for RT-PCR were used: RT-PCR A 70° (hot start); RT-PCR B, 95°C, 60 sec, then 35 cycles (95°m 10 sec, 58°C, 15 sec) then a final 58°C incubation for 7 min, then 4°C and hold. Additional conditions were: primer concentration 0.15 micromolar, template 100 ng/reaction, dNTPs 200 micromolar (final) and $MgCL_2$ 3.5 mM(final). The primers for insert amplification were SEQ ID NOS:28 and 68)

The amplified U3 sequences were purified using Qiaquick. The pVLBPGN plasmid was digested with *Bpm*1, isolated from a 1% agarose gel and purified using the Qiaquick method. The purified U3 sequences were ligated at 1:2, 1:4 and 1:6 molar ratios of VLBPGN plasmid:insert using T4 DNA ligase and a 5 microliter reaction volume overnight at 4°C (100 ng plasmid: 16 ng insert = 1:1 molar ratio). 1 microliter of each ligation reaction was transformed into *E. coli* SCS 110 competent cells (Stratagene). 26 colonies were recovered in total. Out of 23 clones grown overnight in the presence of kanamycin, 20 had sequences that appeared to be mouse VL30 sequences, representing 10 different VL30 species (Fig. 6, SEQ ID NOS: 4-13). One of these (Hep 10, SEQ ID NO: 13) was transiently transfected into Hep G2 liver hepatocellular carcinoma cells. 48 h after transfection, intense GFP fluorescence was observed, indicating strong expression of the Hep 10 U3 promoter region.

Example 4
Creating a combinatorial library of mouse VL30 U3 sub-regions.

Using Fig. 7 and Hodgson, 1996, supra, Fig. 4.2 as a guide, the following three sub-regions of the VL30 U3 region were empirically established: Distal (1); medial (2); and proximal (3). Peaks of similarity were used to guide the following choice of primers: (+) primer binding site-5'-LTR boundary; ~80 bp (defines sub-region 1); ~80-210 bp (sub-region 2); ~210-430 (sub-region 3). The following primers were selected to amplify the vector VLBPGN or a similar VL30, NVL-3 LTR-containing vector:

P1 (going left from the 5'-end of the LTR to amplify the plasmid)

(SEQ ID NO:55)

GACTAACCTTGATTCCACTGGAGTTTT(CT)(CT)ATTCTTCATTCCCCACTTC TTCTT

P2 (going right from the 3'-end of the promoter region to amplify the plasmid)

(SEQ ID NO:56)

GACTAACCTTGATTCCACTGGAGAATCTGGACCAATTCTATATAAGCCTG TGAAAAATTT

The six primers selected to amplify the inserts are as follows:

Fragment 1, primer 1 (going right from the LTR terminus into U3) (SEQ ID NO:57)

GACTAACCTTGATTCCACTGGAGAAGAAGAAGTGGGGAATGAAGAA

Fragment 1, primer 2 (going left from the end of fragment 1) (SEQ ID NO:58)

GACTAACCTTGATTCCACTGGAGATCTCTAGATGGGAGGGG(GT)(CT)GGG CTC

Fragment 2, primer 1 (going right from the left end of fragment 2) (SEQ ID NO:59)

GACTAACCTTGATTCCACTGGAGCTCGGAGCCCACCCCCTCCCATCT

Fragment 2, primer 2 (going left from the right end of fragment 2) (SEQ ID NO:60)

GACTAACCTTGATTCCACTGGAGGGAGGCCCTTATCTCAAAAATGTT

Fragment 3, primer 1 (going right from the left end of fragment 3) (SEQ ID NO:61)

GACTAACCTTGATTCCACTGGAGTCTAAGAACATTTTTGAGATAAGGGCC T

Fragment 3, primer 2 (going left from the right end of fragment 3) (SEQ ID NO:62)

GACTAACCTTGATTCCACTGGAGTCACAGGCTTATATAG(TG)AAA

100 ng of genomic DNA from *Mus musculus* is used as a template (the mouse genome bears 100-200 copies of VL30 elements). Standard PCR procedures for *Pfu* polymerase are used. Fragments are amplified 35 rounds of PCR to obtain single-copy genomic DNA amplification. Samples of Qiagen column purified DNA are examined on analytical agarose gels to determine the approximate size. The remainder of each reaction is digested with the appropriate enzyme and run on an acrylamide or agarose gel. The digested fragments are purified by standard gel purification procedures and are ligated to the plasmid fragment at an equimolar ratio of the four PCR fragments (three inserts and one plasmid). The ligation mix

is transformed into *E. coli* SCS1 and is grown on kanamycin. The number of colonies is used to establish the size of the combinatorial library, and the pooled colonies are grown in *E. coli* and the DNA is harvested *en masse*. A dozen or more colonies are characterized by DNA sequencing to determine the approximate fidelity of the reaction. A library of 1,000 or more, but preferably 100,000 or more members is used for combinatorial screening procedures.

Screening the combinatorial libraries for expression in specific cell types using a replication defective helper virus

The U3 library DNA is transfected into the desired target cells in which expression is desired. Along with the library, approximately 25% of the total DNA should include retroviral helper sequences. The latter sequences can be a helper plasmid (such as pPAM3, Miller *et al.*, US Patent 4,861,719). The virus is amphotropic, permitting it to infect most human cells. The RNA from individual clones that are transcribed in the target cells will be packaged into retroviral virions made by the helper virus, and the virions can be harvested as the cell free filtrate (0.45 mm) from the vector producer cells. This virus (containing the expressed sequences) can be transmitted to fresh target cells that do not contain helper virus. 48 hours after passage, the DNA form of the transcriptionally active clones will be integrated in the recipient cells, and these transcriptionally active loci will produce more RNA, and protein. After G418 drug selection to increase the proportion of cells expressing the vector sequences, helper virus DNA is again transfected into the recipient cells, transforming them into vector producer cells. The virus from these cells should contain increased amounts of the RNA from clones that are transcriptionally active in those cells. Passage of the virus is continued for two or three rounds to permit recombination and mutation to take place, enhancing the effect of *in vitro* evolution of promoters. The actual degree of enhancement attainable at each step is illustrated in Table 2 (*supra*). After several passages, the actual level of RNA expressed by several clones is determined by RNA blotting, or by the amount of a reporter gene expressed as protein (determined visually or by the appropriate assay). Because human cells do not naturally contain VL30 DNA or RNA, the sequences that remain in the human cells are those with the most transcriptionally active promoters. These sequences can be amplified and re-cloned using the methods of the instant invention, or they can be rescued by virus packaging, reverse transcribed by the endogenous reverse

transcriptase reaction, and grown as plasmids (due to their plasmid origin of replication and the selectable kanamycin marker gene).

In addition to using a replication defective helper virus, such as the clone pPAM3, it is also possible to use a replication competent retrovirus, such as Moloney murine leukemia virus to passage the library. For use in human cells, however, the virus should have a tropism that is compatible with human cells (gibbon ape leukemia virus and amphotropic [4070A] murine retroviruses are acceptable).

In addition to being useful for generating active transcriptional promoters *de novo*, a small variation on the above procedures may enable the isolation of hormone responsive promoters. In it, the cells are treated with the hormone (which could be a steroid, a peptide hormone known to affect the cells, a drug, a drug agonist or antagonist, etc.) during passage. After isolation of surviving VL30 vector-containing cells, individual clones of drug resistant cells are tested for reporter gene expression with and without drug treatment to determine relative protein expression. Likewise, RNA expression can be determined by blot analysis or a similar method. A useful list of known VL30 responses to pharmacological agents is listed in Fig. 4.2 of Hodgson, 1996, *supra,* and can be used as a guide to help assess the potential agents known to have an effect on VL30 transcription.

Once the transcriptional promoters with the known specificity have been obtained, they can be used to obtain expression of genes from a variety of types of vectors. For example, in addition to retrovirus particles, the promoters can be incorporated into all other major groups of vectors: adenoviruses, herpes simplex virus vectors, DNA transfection vectors, etc. It will be apparent to persons of ordinary skill in the art that similar combinatorial libraries can also be used to screen for other characteristics than transcription activity in a particular cell. For example, combinatorial libraries of complementarity determining regions (CDRs) of antibodies or T cell receptors can be so screened using antibody screening methods, such as the phage display screening method (Pharmacia, Milwaukee, WI). Thus, the methods of this invention, particularly the combinatorial simplicity of this invention is a significant improvement over many *in vivo* recombination methods including those of (Stemmer, US Patent 5,605,793; 1997) that have described for the production of CDR combinatorial libraries.

Example 5
Gene Assembly Line

From the above examples of 3 and 6 fragment gene self-assemblies, it is evident that assembly of genes by means of gene amplification, the use of offset restriction enzymes and incorporating unique, non-palindromic ends is a highly efficient process compared to conventional cloning methods. However, in addition to the considerations already discussed, it will be apparent to a person of ordinary skill in the art that the various procedures, protocols, methods and material of the instant invention become more difficult to use as the number of fragments increases. For example, if the efficiency of combining each fragment in an assemblage is 99%, then the overall efficiency of combining ten fragments will be 90%, the efficiency of combining 100 fragments will be 37%, etc. Therefore, a small drop in efficiency of any step or fragment, or a large increase in the complexity of the project, will be sufficient to reduce the overall efficiency. Fastidious procedures permit one to achieve success with more complex projects.

Foremost in its potential for inducing failure is human error in primer design where large numbers of fragments are used. Fortunately, the instant invention is suited to automation of most of the steps. This allows human input to be focused on design, analysis, and quality control. For the purposes of generating large vectors or chromosomes, it is desirable to provide an automated environment. One method to achieve this goal is a gene assembly line.

In a gene assembly line, multiple tasks are controlled by a machine or machines working together to increase speed and efficiency and to reduce human error. For example, computer aided design (CAD) and computer aided manufacturing (CAM) are incorporated and combined with the methods of this invention. The computers accept inputs in the form of template and primer sequences, together with preferences of regions to be copied and joined. The preferences include at least the sequences of the primer regions and information about the known restriction sites and maps of the sequences to be assembled, but ideally include the entire sequence. The preferences also include the number of sequences to be joined, the desired Tm for the primers, the list of potential restriction enzymes capable of offset digestion that are potential candidates for use in the assembly process, the desired end structures for each fragment terminus, a tag sequence (if any), whether circular or linear ends

are desired, and additional design considerations. The computer algorithm then searches the sequences to determine the candidate enzymes and specific primers that match the criteria of the input. Candidates for selection of unique non-palindromic overlaps are selected. The computer then posts selections or preferences for the type and order of end structures, the primer binding sites, their potential for primer-dimer and intra-molecular interaction artifacts, and the potential conflicts with repeat sequences within the templates that could lead to incorrect polymerization. Based upon the selections made by the operator, the computer then determine the T_m for each primer, and makes adjustments (with suitable inputs from the investigator) to achieve a suitable T_m for the appropriate DNA synthesis or gene amplification reaction. Ideally, the primers should have similar T_ms so that all amplification reactions can be performed at once with one set of amplification instructions. In reality, it may be difficult to do this with complex projects. The output of this portion of the program, which can be in a generic format, such as a Microsoft Excel spreadsheet is then downloaded to a computerized oligonucleotide synthesizer, such as the Applied Biosystems 3928 nucleic acid synthesizer. One advantage of using a computerized synthesizer is its robotic capability to de-protect and purify the oligonucleotides automatically. In addition this synthesizer can accept computerized input.

The quantity of individual oligos recovered is then determined spectrophotometrically. It is desirable to purify the oligonucleotides by high performance liquid chromatography or by polyacrylamide gel. In a preferred embodiment, the oligonucleotides and templates are then assembled robotically using an automated nucleic acid handling system such as the Qiagen BioRobot 9600. The BioRobot is capable of accepting input from a computer and can combine the gene amplification reactions based upon the assignments of templates, primer and reagents provided in the input. The assembled reactions are then amplified for example by PCR. In a preferred embodiment, the PCR heat block is incorporated into the robotic workspace and genes are assembled robotically but with minimal human intervention to change buffers, rearrange the platform, change programs, and the like. The resulting amplified products are also purified by the BioRobot or a similar robotic device. In a preferred embodiment, the robotic device uses Qiaquick cleanup procedures, or a similar method and then assembles restriction endonuclease reactions to digest the purified gene amplification products. The gene amplification products are loaded onto a gel and electrophoresed. Human intervention may be necessary to analyze the

products and excise the correct fragments from the gel. At this point, the results are assessed and missing or incorrect sized fragments are resynthesized. The robotic device is preferably used to purify the gel fragments using Quiagen or similar cleanup procedures. After spectrophotometric quantitation of the purified fragments, the robotic device is preferably used to assemble the ligation. Ideally the fragments are combined in an equimolar ratio of 1:1. However it is not necessary to use equimolar ratios in order to achieve gene self-assembly. For automated gene assembly, it may be desirable not to use equimolar ratios of input fragments, particularly if it simplified the task of quantitation. After ligation, the assemblies can be purified and ethanol precipitated or they can be added to the appropriate host cells. Automation aids in maintaining the sterility of the reaction.

Several additional considerations can assist in the construction of long genes using gene assembly. First the number of fragments and the length of constructs are limiting factors. In addition to maintaining high standards of purify of both the oligonucleotide primers and gene amplification products, it is important to keep the error rate low during copying. Thus, one can optimally start with 100 ng of template use only five rounds of gene amplification and finish with nearly 2 micrograms of product. This is more desirable for reducing errors than using a large number of amplification steps. It is also desirable to use a special copying enzyme such as *Pfu* DNA polymerase that has a low intrinsic error rate. Further it is desirable to use *in vivo* selection (in eukaryotic cells or tissues) rather than *E. coli* cloning to reduce the incorporation of errors into the vectors. For example, a viral vector such as an adenoviral vector or the retro-vectors of the preceding examples are auto-selecting. A single correctly-assembled adenovirus vector molecule, for example, leads to a lytic infection (the viral products of which are cloned by limiting dilution on the appropriate eukaryotic cells), even though it may be combined in a ligation mix with a large excess of incorrectly assembled molecules that are non-functional. Thus, it is not necessary to have a high efficiency, although high efficiency has been demonstrated in this system, in order to achieve success in making, for example gene therapy vectors.

For long fragments (3-30 kb), it is desirable to use enzymes and procedures that are designed or facilitate replication of long fragments, one such example is the eLONGase system (Life Technologies). This system can copy up to 30 kb on a fragment with proofreading. Considerations for long PCR are reviewed in Beck, 1998. (The Scientist 6 Janary,-1998, pp. 16-18).

Internal restriction sites are a potential problem, particularly with large constructs and can be overcome in a number of ways. Use of alternate enzymes, methylation of internal restrictions sites (such as by using methylated DNA precursors during synthesis to leave the sites in primers unaffected, incorporation of the internal sites into the construct (if they are non-palindromic), or mutagenesis of internal sites, are exemplary ways to deal with some of these issues.

For very large constructs, it is desirable to use enzymes such as *Sap*I (recognizing 7 nucleotides and leaving a 3 bp overhang). This enzyme digests every 16,384 bp on average. There are 64 nucleotide triplet combinations, meaning that up to 32 fragments can be ligated in a circle using *Sap*I. *Fok*1 and *Hga*1 are other examples of class IIS enzymes that are useful for making large constructs. *Hga*1 has 5 bp overhangs, permitting more than 500 *Hga*1 fragments to be ligated. Fok1 includes a Kozak ATG start codon. In a preferred embodiment, a Fok1 site is inserted at the PuXXATG start site of a cDNA encoding region. The cDNA is inserted in frame, providing a site for inserting and switching coding sequences within a vector.

It will be readily understood by those skilled in the art that the foregoing description has been for purposes of illustration only and that a variety of embodiments can be envisioned without departing from the scope of the invention. Therefore, it is intended that the invention not be limited except by the claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: NATURE TECHNOLOGY CORPORATION, ET AL.

(ii) TITLE OF INVENTION: SELF-ASSEMBLING GENES, VECTORS AND USES THEREOF

(iii) NUMBER OF SEQUENCES: 68

(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: MUETING, RAASCH & GEBHARDT, P.A.
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(C) CITY: MINNEAPOLIS
(D) STATE: MINNESOTA
(E) COUNTRY: USA
(F) ZIP: 55401

(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Floppy disk
(B) COMPUTER: IBM PC compatible
(C) OPERATING SYSTEM: PC-DOS/MS-DOS
(D) SOFTWARE: PatentIn Release #1.0, Version #1.30

(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: Not Assigned
(B) FILING DATE: 28-FEB-1998
(C) CLASSIFICATION:

(vii) PRIORITY APPLICATION DATA:
(A) APPLICATION NUMBER: 60/070,910
(B) FILING DATE: 28-FEB-1997
(C) CLASSIFICATION:

(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: MCCORMACK, MYRA M.
(B) REGISTRATION NUMBER: 36,602
(C) REFERENCE/DOCKET NUMBER: 228.00010201

(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: 612-305-1225
(B) TELEFAX: 612-305-1228

(2) INFORMATION FOR SEQ ID NO:1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6225 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:1:

TGAAGAATAA AAAATTACTG GCCTCTTGTG AGAACATGAA CTTTCACCTC GGAGCCCACC 60

CCCTCCCATC TGGAAAACTC CAGTTATAAC TGGAGTTTTT CCTTTAAAAG CTTGTGAAAA 120
ATTTGAGTCG TCGTCGAGAC TCCTCTACCC TGTGCAAAGG TGTATGAGTT TCGACCCCAG 180

AGCTCTGTGT GCTTTCTGTT GCTGCTTTAT TTCGACCCCA GAGCTCTGGT CTGTGTGCTT 240

TCATGTCGCT GCTTTATTAA ATCTTACCTT CTACATTTTA TGTATGGTCT CAGTGTCTTC 300

TTGGGTACGC GGCTGTCCCG GGACTTGAGT GTCTGAGTGA GGGTCTTCCC TCGAGGGTCT 360

TTCATTTGGT ACATGGGCCG GGAATTCGAG AATCTTTCAT TTGGTGCATT GGCCGGGAAT 420

TCGAAAATCT TTCATTTGGT GCATTGGCCG GGAAACAGCG CGACCACCCA GAGGTCCTAG 480

ACCCACTTAG AGGTAAGATT CTTTGTTCTG TTTTGGTCTG ATGTCTGTGT TCTGATGTCT 540

GTGTTCTGTT TCTAAGTCTG GTGCGATCGC AGTTTCAGTT TTGCGGACGC TCAGTGAGAC 600

CGCGCTCCGA GAGGGAGTGC GGGGTGGATA AGGATAGACG TGTCCAGGTG TCCACCGTCC 660

GTTCGCCCTG GGAGACGTCC CAGGAGGAAC AGGGGAGGAT CAGGGACGCC TGGTGGACCC 720

CTTTGAAGGC CAAGAGACCA TTTGGGGTTG CGAGATCGTG GGTTCGAGTC CCACCTCGTG 780

CCCAGTTGCG AGATCGTGGG TTCGAGTCCC ACCTCGTGTT TTGTTGCGAG ATCGTGGGTT 840

CGAGTCCCAC CTCGCGTCTG GTCACGGGAT CGTGGGTTCG AGTCCCACCT CGTGTTTTGT 900

TGCGAGATCG TGGGTTCGAG TCCCACCTCG CGTCTGGTCA CGGGATCGTG GGTTCGAGTC 960

CCACCTCGTG CAGAGGGTCT CAATTGGCCG GCCTTAGAGA GGCCATCTGA TTCTTCTGGT 1020

TTCTCTTTTT GTCTTAGTCT CGTGTCCGCT CTTGTTGTGA CTACTGTTTT TCTAAAAATG 1080

GGACAATCTG TGTCCACTCC CCTTTCTCTG ACTCTGGTTC TGTCGCTTGG TAATTTTGTT 1140

TGTTTACGTT TGTTTTTGTG AGTCGTCTAT GTTGTCTGTT ACTATCTTGT TTTTGTTTGT 1200

GGTTTACGGT TTCTGTGTGT GTCTTGTGTG TCTCTTTGTG TTCAGACTTG GACTGATGAC 1260

TGACGACTGT TTTTAAGTTA TGCCTTCTAA AATAAGCCTA AAAATCCTGT CAGATCCCTA 1320

TGCTGACCAC TTCCTTTCAG ATCAACAGCT GCCCTTACTC GAGCTCAAGC TTCGAATTCT 1380

GCAGTCGACG GTACCGCGGC CGCTAACTAA TAGCCCATTC TCCAAGGTAC GTAGCGGGGA 1440

TCAATTCCGC CCCCCCCCTA ACGTTACTGG CCGAAGCCGC TTGGAATAAG GCCGGTGTGC 1500

GTTTGTCTAT ATGTTATTTT CCACCATATT GCCGTCTTTT GGCAATGTGA GGGCCCGGAA 1560

ACCTGGCCCT GTCTTCTTGA CGAGCATTCC TAGGGGTCTT TCCCCTCTCG CCAAAGGAAT 1620

GCAAGGTCTG TTGAATGTCG TGAAGGAAGC AGTTCCTCTG GAAGCTTCTT GAAGACAAAC 1680

AACGTCTGTA GCGACCCTTT GCAGGCAGCG GAACCCCCCA CCTGGCGACA GGTGCCTCTG 1740

CGGCCAAAAG CCACGTGTAT AAGATACACC TGCAAAGGCG GCACAACCCC AGTGCCACGT 1800

TGTGAGTTGG ATAGTTGTGG AAAGAGTCAA ATGGCTCTCC TCAAGCGTAT TCAACAAGGG 1860

GCTGAAGGAT GCCCAGAAGG TACCCCATTG TATGGGATCT GATCTGGGGC CTCGGTGCAC 1920

ATGCTTTACA TGTGTTTAGT CGAGGTTAAA AAAACGTCTA GGCCCCCCGA ACCACGGGGA 1980

CGTGGTTTTC CTTTGAAAAA CACGATACGG GATCCACCGG TCGCCACCAT GGGTAAAGGA 2040

GAAGAACTTT TCACAGGAGT TGTCCCAATT CTTGTTGAAT TAGATGGTGA TGTTAATGGG 2100

CACAAATTTT CTGTCAGTGG AGAGGGTGAA GGTGATGCAA CATACGGAAA ACTTACCCTT 2160

AAATTTATTT GCACTACTGG AAAACTACCT GTTCCATGGC CAACACTTGT CACTACTTTC 2220

ACTTATGGTG TTCAATGCTT TTCAAGATAC CCAGATCATA TGAAACGGCA TGACTTTTTC 2280

AAGAGTGCCA TGCCCGAAGG TTATGTACAG GAAAGAACTA TATTTTTCAA AGATGACGGG 2340

AACTACAAGA CACGTGCTGA AGTCAAGTTT GAAGGTGATA CCCTTGTTAA TAGAATCGAG 2400

TTAAAAGGTA TTGATTTTAA AGAAGATGGA AACATTCTTG GACACAAATT GGAATACAAC 2460

TATAACTCAC ACAATGTATA CATCATGGCA GACAAACAAA AGAATGGAAC CAAAGTTAAC 2520

TTCAAAATTA GACACAACAT TGAAGATGGA AGCGTTCAAC TAGCAGACCA TTATCAACAA 2580

AATACTCCAA TTGGCGATGG CCCTGTCCTT TTACCAGACA ACCATTACCT GTCCACACAA 2640

TCTGCCCTTT CGAAAGATCC CAACGAAAAG AGAGACCACA TGGTCCTTCT TGAGTTTGTA 2700

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TATCGATGGA TCCGAAGGCG GGGACAGCAG TGCAGTGGTG GACAGAAAGC AAGTGATCTA 2820

GGCCAGCAGC CTCCCTAAAG GGACTTCAGC CCACAAAGCC AAACTTGTGG CTTTAATACA 2880

AGCTCTGTAA ATGGTAAAAA AAAAAAAGTC TACACGGACA GCAGGTATGC TCTTGCCACT 2940

GTACAGAGCA ATATACAGAC AAAGAGAACT GTTGACATCT GCAGAGAAAG ACCTAAGATG 3000

CTGTGGCTAA AAGAAATCAG ATGGCAAATC TAACCGCCCA GGCATCCTAA AGAGCAATGA 3060

TCCTGACAGT CTGAAGACTA TCAAGTTATA GACAAATTAA GACTGGTAAA AAAAACCCTG 3120

TATAAAATAG TAAAAACTGA AAAAAGAAAA CTAGTCCTCT CATGAGAAGA CAGACCTGAC 3180

ATCTACTGAA AAATAGACTT TACTGGAAAA AATATGTGTA TGAATACCTT CTAGTTTTTG 3240

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TCAAGAAGAT TGTTAAAGAA AATTTTCCAA GGTTCGGAGT GCCAAAAGCA ATAGTGTCAG 3360

ATAATGGTCC TGCCTTTGTT GCCCAGGTAA GTCAGGGTGT GGCCAAGTAT TTAGAGGTCA 3420

AATGAAAATT CCATTGTGTG TACAGACCTC AGAGCTCAGG AAAGATAAAA AAGAATAAAT 3480

AAAACTCTAA ACAGACCTTG ACAAAATTAA TCCTAGAGAC TGGCACAGAC TTACTTGGTA 3540

CTCCTTCCCC TTGCCCTATT TAGAACTGAG AATACTCCCT CTTGATTCGG TTTTACTCTT 3600

TTTAAGATCC TTTATGGGGC TCCTATGCCA TCACTGTCTT AAATGATGTG TTTAAACCTA 3660

TGTTGTTATA ATAATGATCT ATATGTTAAG TTAAAAGGCT TGCAGGTGGT GCAGAAAGAA 3720

GTCTGGTCAC AACTGGCTAC AGTGAACAAG CTGGGTACCC CAAGGACATC TTACCAGTTC 3780

CAGCCAGAGA TCTGATCTAC GATCCCCGGG TCGACCCGGG TCGACCCTGT GGAATGTGTG 3840

TCAGTTAGGG TGTGGAAAGT CCCCAGGCTC CCCAGCAGGC AGAAGTATGC AAAGCATGCA 3900

TCTCAATTAG TCAGCAACCA GGTGTGGAAA GTCCCCAGGC TCCCCAGCAG GCAGAAGTAT 3960

GCAAAGCATG CATCTCAATT AGTCAGCAAC CATAGTCCCG CCCCTAACTC CGCCCATCCC 4020

GCCCCTAACT CCGCCCAGTT CCGCCCATTC TCCGCCCCAT GGCTGACTAA TTTTTTTTAT 4080
TTATGCAGAG GCCGAGGCCG CCTCGGCCTC TGAGCTATTC CAGAAGTAGT GAGGAGGCTT 4140

TTTTGGAGGC CTAGGCTTTT GCAAAAAGCT TCACGCTGCC GCAAGCACTC AGGGCGCAAG 4200

GGCTGCTAAA GGAAGCGGAA CACGTAGAAA GCCAGTCCGC AGAAACGGTG CTGACCCCGG 4260

ATGAATGTCA GCTACTGGGC TATCTGGACA AGGGAAAACG CAAGCGCAAA GAGAAAGCAG 4320

GTAGCTTGCA GTGGGCTTAC ATGGCGATAG CTAGACTGGG CGGTTTTATG GACAGCAAGC 4380

GAACCGGAAT TGCCAGCTGG GGCGCCCTCT GGTAAGGTTG GGAAGCCCTG CAAAGTAAAC 4440

TGGATGGCTT TCTTGCCGCC AAGGATCTGA TGGCGCAGGG GATCAAGATC TGATCAAGAG 4500

ACAGGATGAG GATCGTTTCG CATGATTGAA CAAGATGGAT TGCACGCAGG TTCTCCGGCC 4560

GCTTGGGTGG AGAGGCTATT CGGCTATGAC TGGGCACAAC AGACAATCGG CTGCTCTGAT 4620

GCCGCCGTGT TCCGGCTGTC AGCGCAGGGG CGCCCGGTTC TTTTTGTCAA GACCGACCTG 4680

TCCGGTGCCC TGAATGAACT GCAGGACGAG GCAGCGCGGC TATCGTGGCT GGCCACGACG 4740

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CTCAAGGCGC GCATGCCCGA CGGCGAGGAT CTCGTCGTGA CCCATGGCGA TGCCTGCTTG 5100

CCGAATATCA TGGTGGAAAA TGGCCGCTTT TCTGGATTCA TCGACTGTGG CCGGCTGGGT 5160

GTGGCGGACC GCTATCAGGA CATAGCGTTG GCTACCCGTG ATATTGCTGA AGAGCTTGGC 5220

GGCGAATGGG CTGACCGCTT CCTCGTGCTT TACGGTATCG CCGCTCCCGA TTCGCAGCGC 5280

ATCGCCTTCT ATCGCCTTCT TGACGAGTTC TTCTGAGCGG GACTCTGGGG TTCGAAATGA 5340

CCGACCAAGC GACGCCCAAC CTGCCATCAC GAGATTTCGA TTCCACCGCC GCCTTCTATG 5400

AAAGGTTGGG CTTCGGAATC GTTTTCCGGG ACGGAATTCG TAATCTGCTG CTTGCAAACA 5460

AAAAAACCAC CGCTACCAGC GGTGGTTTGT TTGCCGGATC AAGAGCTACC AACTCTTTTT 5520

CCGAAGGTAA CTGGCTTCAG CAGAGCGCAG ATACCAAATA CTGTCCTTCT AGTGTAGCCG 5580

TAGTTAGGCC ACCACTTCAA GAACTCTGTA GCACCGCCTA CATACCTCGC TCTGCTAATC 5640

CTGTTACCAG TGGCTGCTGC CAGTGGCGAT AAGTCGTGTC TTACCGGGTT GGACTCAAGA 5700

CGATAGTTAC CGGATAAGGC GCAGCGGTCG GGCTGAACGG GGGGTTCGTG CACACAGCCC 5760

AGCTTGGAGC GAACGACCTA CACCGAACTG AGATACCTAC AGCGTGAGCA TTGAGAAAGC 5820

GCCACGCTTC CCGAAGGGAG AAAGGCGGAC AGGTATCCGG TAAGCGGCAG GGTCGGAACA 5880

GGAGAGCGCA CGAGGGAGCT TCCAGGGGGA AACGCCTGGT ATCTTTATAG TCCTGTCGGG 5940

TTTCGCCACC TCTGACTTGA GCGTCGATTT TTGTGATGCT CGTCAGGGGG GCGGAGCCTA 6000

TGGAAAAACG CCAGCAACGC CGAGATGCGC CGCCTCGAGT ACACCTGCGT CATGCTGAGA 6060
CCCTCAAGCC TCACTAAAAG GGTCCCTGCC TAGTTCTGTT TACTAATCTG CCTTATTCTG 6120

TTTTTGTTCC CATGTTAAAG ATAGAGTAAA TGCAGTATTC TCCACATAGA GATATAGACT 6180

TCTGAAATTC TAAGATTAGA ATTATTTACA AGAAGAAGTG GGGAA 6225-

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 487 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:2:

CCTCCCATCT AGAGGTTGTT CTCGGAACAC TCCTAAACTT TTCACCCCAA AACTCCTCAC 60

CCTAAAGTTC GAAAAAACTG TTCCAAGAAC ATTTTTGAGA TAAAGGCCTC CTAGAACAAC 120

CTCAAAATGA CATTGCCAAA TGATAAGACA TGACTCCTTA GTTACGTAGG TTCCTTGATA 180

GGACATGACT CCTTAGTTAC GTAGGTTCCT TGATAGGACA TGACTCCTTA GTTACGTAGA 240

TTCCTTTGGT AGAACTCCCT AGTGATGTAA ACTTGTACTT TCCCTGCCCA GTTCTCCCCC 300

TTTGAGTTTT ACTATATAAG CCTGTAAAAA ATTTTTGCTG ACCGTCGAGA CTCCTCTACC 360

CTGTGCTAAG GTGTATGAGT TTCGACCCCA GAGCTCTGTG TGCTTCCATG TTGCTGCTTT 420

ATTTCGACCC CAGAGCTCTG GTCTGTGTGC TTTCATGTCG CTGCTTTATT AAATCTTGCC 480

TTCTACA 487

(2) INFORMATION FOR SEQ ID NO:3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 366 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

CCTCCCATCT AGAAAACATT TTTGAGATAA AGGCTTCCTG GAACAACCTC AAAATGAACC 60

AGGTACTCCT TAGTTACGTA GGTTCCTTGA TAGGACATGA CTCCTTAGTT ACATAGATTC 120

CTTTGGCAGA ACTCCCTAGT GATGTAAACT TGTACTTTCC CTGCCCAGTT CTCCCCCTTT 180

GAGTTTTACT ATATAAGCCT GTGAAAAATT TTGGCTGACC GTCGAGACTC CTCTACCCTG 240

TGCTAAGGTG TATGAGTTTC GACCCCAGAG CTCTGTGTGC TTCCATGTTG CTGCTTTATT 300

TCGACCCCAG AGCTCTGGTC TGTGTGCTTT CATGTTGCTG CCTTATTAAA TCTTGCCTTC 360
TACATT 366

(2) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 304 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

CCTCCCATCT AGAGATTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATGCC 60
TGAACTCCTC ACCCTAGAGT TCGAACCCTC CCAACTAAAG ACTGTTCCAA GAACATTTTT 120
GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGG TACATTGCCA AATAATAGGA 180
CATGACCCCT TAGTTACGTA AAATCCCTTG GCAGAACCCC TTGTCCCTTG GCAGAACCCC 240
TTAGTTATGT AAACTTGTAC TTTCCCTACC CCGCTCTCCC CCCTTGAGTT TTTCCTATAT 300
AAGC 304

(2) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 304 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC 60
TGAACTCCTC ACCCTAGAGT TCGAACCCTC CCAACTAAAG ACTGTTCCAA GAACATTTTT 120
GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGA TACATTGCCA AATAATAGGA 180
CATGACCCCT TAGTTACGTA GAATCCCTTG GCAGAACCCC TTGTCCCTTG GCAGAACCCC 240
TTAGTTATGT AAACTTGTAC TTTCCCTACC CCGCTCTCCC CCCTTGAGTT TTTCCTATAT 300
AAGC 304

(2) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 304 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC 60

TGAACTCCTC ATCCTAGAGT TCGAACCCTC CCAACTAAAG ACTGTTCCAA GAACATTTTT 120

GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCTGG TACATTGCCA AATAATAGGA 180

CATGACCCTT TAGTTACGTA GAATCCCTTG GCAGAACCCC TTGTCCCTTG GCAGAACCCC 240

TTAGTTATGC AAACTTGTAC TTTCTCTGCC CCGCTCTCCC CCCTTGAGTT TTTCCTATAT 300

AAGC 304

(2) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 304 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:7:

CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCACCTCAA AATGCATTCC 60

TGAACTCCTC ACCCTAGAGT TCGAACCCTC CCAACTAAAG ACTGTTCCAA GAACATTTTT 120

GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCAGG TACATTGCCA AATAATAGGA 180

CATGACCCTT TAGTTACGTA GAATCCCTTG GCAGAACCCC TTGTCCCTTG GCAGAACCCC 240

TTAGTTATGC AAACTTGTAC TTTCTCTGCC CCGCTCTCCC CCCTTGAGTT TTTCCTATAT 300

AAGC 304

(2) INFORMATION FOR SEQ ID NO:8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 305 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:8:

CCTCCCATCT AGAGATTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC 60

TGAACTCCTC ACCCTAGAGT TCGAACCCTC CCAACTAAAG ACTGTTCCAA GAACATTTTT 120

GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGA TACATTGCCA AATAATAGGA 180

CATGACCCCT TAGTTACGTA GAATTCCCTT GGCAGAACCC CTTGTCCCTT GGCAGAACCC 240

CTTAGTTATG CAAACTTGTA CTTTCCCTGC CCCGCTCTCC CCCCTTGAGG TTTTCCTATA 300

TAAGC 305

(2) INFORMATION FOR SEQ ID NO:9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 305 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:9:

CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC 60

TGAACCCCTC ACCCTAGAGT TCGAACCCTC CCAACTAAAG ACTGTTCCAA GAACATTTTT 120

GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCAGG TACATTGCCA AATAATAGGA 180

CATGACCCCT TAGTTACGTA GAATTCCCTT GGCAGAACCC CTTGTCCCTT GGCAGAACCC 240

CTTAGTTATG CGAACTTGTA CTTTCCCTGC CCCGCTCTCC CCCCTTGAGT TTTTCCTATA 300

TAAGC 305

(2) INFORMATION FOR SEQ ID NO:10:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 306 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:10:

CCCTCCCATC TAGAGAGTGT TCCCAGAACA CTCCTGAACT CTTCATCCCA GAATGCATTC 60

CTGAACTCCT CACCCTATAG TTCGAACCCT CCCAACTAAA GACTGTTCCA AGAACATTTT 120

TGAGATAAGG GCCTCCTGGA ACAACCTCAG AATGAACCGG GTACATTGCC AAATAATAGG 180

ACATGACCCC TTAGTTACGT AGAATTCCCT TGGCAGAACC CCTTGTCGCT TGGCAGAACC 240

CCTTAGTTAT GTAAACTTGT ACTTTCCCTG CCCCGCTCTC CCCCCTTGAG TTTTTACTAT 300

ATAAGC 306

(2) INFORMATION FOR SEQ ID NO:11:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 305 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:11:

CCTCCCATCT AGAGAGTGTT CCCAAAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC 60

TGAACTCCTC ACCCTAAAGT TCAAACCCTC CCAACTAAAG ACTGTTCCAA GAACATTTTT 120

GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGG TACATTGCCA AATAATAGGA 180

CATGACCCCT TAGTTACACA GAATTCCCTT GGCAAAACCC CTTGTCCCTT GGCAGAACCC 240

CTTAGTTATG CAAACTTGTA CTTTCCCTGC CCAGCTCTCC CCCCTTGAGT TTTTCCTATA 300

TAAGC 305

(2) INFORMATION FOR SEQ ID NO:12:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 304 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:12:

CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC 60

TGAACTCCTC ACCCTAGAGT TTGAACCCTC CCAACTAAAG ACTGTTCCAA GAACATCTTT 120

GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGG TACATTGCCA AATAATAGGA 180

CATGACCCCT TAGTTACGTA GAATTCCCTT GGCAGAACCC CTTGTCGCTT GGCAGAACCC 240

CTTAGTTATG CAAACTTGTA CTTTCCCTGC CCCGCTCTCC CCCTTGAGTT TTTCCTATAT 300

AAGC 304

(2) INFORMATION FOR SEQ ID NO:13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 303 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:13:

CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTAAACTC TTCACCCCAG AATGCATTCC 60
TGAACTCCTC ACCCTAGAGT TCGAACCCTT CCAACTAAAG ACTGTTCCAA GAACATTTTT 120

GAGATAAGGG CCTCCTGGAA CAACCTCAAA ATGAACCGGG TACATTGCCA AATGATAGGA 180

CATGACCCCT TAGTTACGTA GATTCCCTTG GCAGAACCCC TTGTCCCTTG GCAGAACCCC 240

CTAGTGATGT AAACTTGTAC TTTCCCTGCC CAGCTCTCCC CCCTTGAGTT TTCCTATATA 300

AGC 303

(2) INFORMATION FOR SEQ ID NO:14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 8657 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:14:

TGAAGAATAA AAAATTACTG GCCTCTTGTG AGAACATGAA CTTTCACCTC GGAGCCCACC 60

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TTGTTAAACT TCCCCTATTC CCTCCCCATT CCCCCTCCCA GTTTGTGGTT TTTTCCTTTA 240

AAAGCTTGTG AAAAATTTGA GTCGTCGTCG AGACTCCTCT ACCCTGTGCA AAGGTGTATG 300

AGTTTCGACC CCAGAGCTCT GTGTGCTTTC TGTTGCTGCT TTATTTCGAC CCCAGAGCTC 360

TGGTCTGTGT GCTTTCATGT CGCTGCTTTA TTAAATCTTA CCTTCTACAT TTTATGTATG 420

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TCCCTCGAGG GTCTTTCATT TGGTACATGG GCCGGGAATT CGAGAATCTT TCATTTGGTG 540

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CGCCTGGTGG ACCCCTTTGA AGGCCAAGAG ACCATTTGGG GTTGCGAGAT CGTGGGTTCG 900

AGTCCCACCT CGTGCCCAGT TGCGAGATCG TGGGTTCGAG TCCCACCTCG TGTTTTGTTG 960

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CTGATTCTTC TGGTTTCTCT TTTTGTCTTA GTCTCGTGTC CGCTCTTGTT GTGACTACTG 1200

TTTTTCTAAA AATGGGACAA TCTGTGTCCA CTCCCCTTTC TCTGACTCTG GTTCTGTCGC 1260

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CCCCTAACGT TACTGGCCGA AGCCGCTTGG AATAAGGCCG GTGTGCGTTT GTCTATATGT 1620

TATTTTCCAC CATATTGCCG TCTTTTGGCA ATGTGAGGGC CCGGAAACCT GGCCCTGTCT 1680

TCTTGACGAG CATTCCTAGG GGTCTTTCCC CTCTCGCCAA AGGAATGCAA GGTCTGTTGA 1740

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GCAGCAGTGG CGTCTGGCGG AAAACCTCAG TGTGACGCTC CCCGCCGCGT CCCACGCCAT 4320

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ATTTAACCGC CAGTCAGGCT TTCTTTCACA GATGTGGATT GGCGATAAAA AACAACTGCT 4440

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GACCGCTCAC GCGTGGCAGC ATCAGGGGAA AACCTTATTT ATCAGCCGGA AAACCTACCG 4680

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TTTACGGTAT CGCCGCTCCC GATTCGCAGC GCATCGCCTT CTATCGCCTT CTTGACGAGT 7740

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GAAACGCCTG GTATCTTTAT AGTCCTGTCG GGTTTCGCCA CCTCTGACTT GAGCGTCGAT 8400

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CAAGAAGAAG TGGGGAA 8657

(2) INFORMATION FOR SEQ ID NO:15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6359 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:15:

TGAAGAATAA AAAATTACTG GCCTCTTGTG AGAACATGAA CTTTCACCTC GGAGCCCACC 60

CCCTCCCATC TGGAAAACAT ACTTGAGAAA AACATTTTCT GGAACAACCA CAGAATGTTT 120

CAACAGGCCA GATGTATTGC CAAACACAGG ATATGACTCT TTGGTTGAGT AAATTTGTGG 180

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GACAGGTGCC TCTGCGGCCA AAAGCCACGT GTATAAGATA CACCTGCAAA GGCGGCACAA 1920
CCCCAGTGCC ACGTTGTGAG TTGGATAGTT GTGGAAAGAG TCAAATGGCT CTCCTCAAGC 1980

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CAGGTTCTCC GGCCGCTTGG GTGGAGAGGC TATTCGGCTA TGACTGGGCA CAACAGACAA 4740

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TTCTAGTGTA GCCGTAGTTA GGCCACCACT TCAAGAACTC TGTAGCACCG CCTACATACC 5760

TCGCTCTGCT AATCCTGTTA CCAGTGGCTG CTGCCAGTGG CGATAAGTCG TGTCTTACCG 5820

GGTTGGACTC AAGACGATAG TTACCGGATA AGGCGCAGCG GTCGGGCTGA ACGGGGGGTT 5880
CGTGCACACA GCCCAGCTTG GAGCGAACGA CCTACACCGA ACTGAGATAC CTACAGCGTG 5940

AGCATTGAGA AAGCGCCACG CTTCCCGAAG GGAGAAAGGC GGACAGGTAT CCGGTAAGCG 6000

GCAGGGTCGG AACAGGAGAG CGCACGAGGG AGCTTCCAGG GGGAAACGCC TGGTATCTTT 6060

ATAGTCCTGT CGGGTTTCGC CACCTCTGAC TTGAGCGTCG ATTTTTGTGA TGCTCGTCAG 6120

GGGGGCGGAG CCTATGGAAA AACGCCAGCA ACGCCGAGAT GCGCCGCCTC GAGTACACCT 6180

GCGTCATGCT GAGACCCTCA AGCCTCACTA AAAGGGTCCC TGCCTAGTTC TGTTTACTAA 6240

TCTGCCTTAT TCTGTTTTTG TTCCCATGTT AAAGATAGAG TAAATGCAGT ATTCTCCACA 6300

TAGAGATATA GACTTCTGAA ATTCTAAGAT TAGAATTATT TACAAGAAGA AGTGGGGAA 6359

(2) INFORMATION FOR SEQ ID NO:16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6891 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:16:

TGAAGAATAA AAAATTACTG GCCTCTTGTG AGAACATGAA CTTTCACCTC GGAGCCCACC 60
CCCTCCCATC TGGAAAACAT ACTTGAGAAA AACATTTTCT GGAACAACCA CAGAATGTTT 120
CAACAGGCCA GATGTATTGC CAAACACAGG ATATGACTCT TTGGTTGAGT AAATTTGTGG 180
TTGTTAAACT TCCCCTATTC CCTCCCCATT CCCCCTCCCA GTTTGTGGTT TTTTCCTTTA 240
AAAGCTTGTG AAAAATTTGA GTCGTCGTCG AGACTCCTCT ACCCTGTGCA AAGGTGTATG 300
AGTTTCGACC CCAGAGCTCT GTGTGCTTTC TGTTGCTGCT TTATTTCGAC CCCAGAGCTC 360
TGGTCTGTGT GCTTTCATGT CGCTGCTTTA TTAAATCTTA CCTTCTACAT TTTATGTATG 420
GTCTCAGTGT CTTCTTGGGT ACGCGGCTGT CCCGGGACTT GAGTGTCTGA GTGAGGGTCT 480
TCCCTCGAGG GTCTTTCATT TGGTACATGG GCCGGGAATT CGAGAATCTT TCATTTGGTG 540
CATTGGCCGG GAATTCGAAA ATCTTTCATT TGGTGCATTG GCCGGGAAAC AGCGCGACCA 600
CCCAGAGGTC CTAGACCCAC TTAGAGGTAA GATTCTTTGT TCTGTTTTGG TCTGATGTCT 660
GTGTTCTGAT GTCTGTGTTC TGTTTCTAAG TCTGGTGCGA TCGCAGTTTC AGTTTTGCGG 720
ACGCTCAGTG AGACCGCGCT CCGAGAGGGA GTGCGGGGTG GATAAGGATA GACGTGTCCA 780
GGTGTCCACC GTCCGTTCGC CCTGGGAGAC GTCCCAGGAG GAACAGGGGA GGATCAGGGA 840
CGCCTGGTGG ACCCCTTTGA AGGCCAAGAG ACCATTTGGG GTTGCGAGAT CGTGGGTTCG 900
AGTCCCACCT CGTGCCCAGT TGCGAGATCG TGGGTTCGAG TCCCACCTCG TGTTTTGTTG 960
CGAGATCGTG GGTTCGAGTC CCACCTCGCG TCTGGTCACG GGATCGTGGG TTCGAGTCCC 1020
ACCTCGTGTT TTGTTGCGAG ATCGTGGGTT CGAGTCCCAC CTCGCGTCTG GTCACGGGAT 1080
CGTGGGTTCG AGTCCCACCT CGTGCAGAGG GTCTCAATTG GCCGGCCTTA GAGAGGCCAT 1140
CTGATTCTTC TGGTTTCTCT TTTTGTCTTA GTCTCGTGTC CGCTCTTGTT GTGACTACTG 1200
TTTTTCTAAA AATGGGACAA TCTGTGTCCA CTCCCCTTTC TCTGACTCTG GTTCTGTCGC 1260
TTGGTAATTT TGTTTGTTTA CGTTTGTTTT TGTGAGTCGT CTATGTTGTC TGTTACTATC 1320
TTGTTTTTGT TTGTGGTTTA CGGTTTCTGT GTGTGTCTTG TGTGTCTCTT TGTGTTCAGA 1380
CTTGGACTGA TGACTGACGA CTGTTTTTAA GTTATGCCTT CTAAAATAAG CCTAAAAATC 1440
CTGTCAGATC CCTATGCTGA CCACTTCCTT TCAGATCAAC AGCTGCCCTT ACTCGAGCTC 1500
AAGCTTCGAA TTCTGCAGTC GACGGTACCG CGGGGATCAA TTCCGCCCCC CCCCTAACGT 1560

TACTGGCCGA AGCCGCTTGG AATAAGGCCG GTGTGCGTTT GTCTATATGT TATTTTCCAC 1620

CATATTGCCG TCTTTTGGCA ATGTGAGGGC CCGGAAACCT GGCCCTGTCT TCTTGACGAG 1680

CATTCCTAGG GGTCTTTCCC CTCTCGCCAA AGGAATGCAA GGTCTGTTGA ATGTCGTGAA 1740

GGAAGCAGTT CCTCTGGAAG CTTCTTGAAG ACAAACAACG TCTGTAGCGA CCCTTTGCAG 1800

GCAGCGGAAC CCCCCACCTG GCGACAGGTG CCTCTGCGGC CAAAAGCCAC GTGTATAAGA 1860

TACACCTGCA AAGGCGGCAC AACCCCAGTG CCACGTTGTG AGTTGGATAG TTGTGGAAAG 1920

AGTCAAATGG CTCTCCTCAA GCGTATTCAA CAAGGGGCTG AAGGATGCCC AGAAGGTACC 1980

CCATTGTATG GGATCTGATC TGGGGCCTCG GTGCACATGC TTTACATGTG TTTAGTCGAG 2040

GTTAAAAAAC GTCTAGGCCC CCCGAACCAC GGGGACGTGG TTTTCCTTTG AAAAACACGA 2100

GCGGGATCAA TTCCGCCCCC CCCCTAACGT TACTGGCCGA AGCCGCTTGG AATAAGGCCG 2160

GTGTGCGTTT GTCTATATGT TATTTTCCAC CATATTGCCG TCTTTTGGCA ATGTGAGGGC 2220

CCGGAAACCT GGCCCTGTCT TCTTGACGAG CATTCCTAGG GGTCTTTCCC CTCTCGCCAA 2280

AGGAATGCAA GGTCTGTTGA ATGTCGTGAA GGAAGCAGTT CCTCTGGAAG CTTCTTGAAG 2340

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CCTCTGCGGC CAAAAGCCAC GTGTATAAGA TACACCTGCA AAGGCGGCAC AACCCCAGTG 2460

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CAAGGGGCTG AAGGATGCCC AGAAGGTACC CCATTGTATG GGATCTGATC TGGGGCCTCG 2580

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CGGGGACGTG GTTTTCCTTT GAAAAACACG ATACGGGATC CACCGGTCGC CACCATGGGT 2700

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ACCCTTAAAT TTATTTGCAC TACTGGAAAA CTACCTGTTC CATGGCCAAC ACTTGTCACT 2880

ACTTTCACTT ATGGTGTTCA ATGCTTTTCA AGATACCCAG ATCATATGAA ACGGCATGAC 2940

TTTTTCAAGA GTGCCATGCC CGAAGGTTAT GTACAGGAAA GAACTATATT TTTCAAAGAT 3000
GACGGGAACT ACAAGACACG TGCTGAAGTC AAGTTTGAAG GTGATACCCT TGTTAATAGA 3060

ATCGAGTTAA AAGGTATTGA TTTTAAAGAA GATGGAAACA TTCTTGGACA CAAATTGGAA 3120

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TTTGTAACAG CTGCTGGGAT TACACATGGC ATGGATGAAC TATACAAGTC CGGATCTAGA 3420

TAACTGTATC GATGGATCCG AAGGCGGGGA CAGCAGTGCA GTGGTGGACA GAAAGCAAGT 3480

GATCTAGGCC AGCAGCCTCC CTAAAGGGAC TTCAGCCCAC AAAGCCAAAC TTGTGGCTTT 3540

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TTTTTGTGAA CGTTCTCAAG ATGGATAAAA GCTTTTCCTT GTAAAACGAG ACTGATCAGA 3960

TAGTCATCAA GAAGATTGTT AAAGAAAATT TTCCAAGGTT CGGAGTGCCA AAAGCAATAG 4020

TGTCAGATAA TGGTCCTGCC TTTGTTGCCC AGGTAAGTCA GGGTGTGGCC AAGTATTTAG 4080

AGGTCAAATG AAAATTCCAT TGTGTGTACA GACCTCAGAG CTCAGGAAAG ATAAAAAAGA 4140

ATAAATAAAA CTCTAAACAG ACCTTGACAA AATTAATCCT AGAGACTGGC ACAGACTTAC 4200

TTGGTACTCC TTCCCCTTGC CCTATTTAGA ACTGAGAATA CTCCCTCTTG ATTCGGTTTT 4260

ACTCTTTTTA AGATCCTTTA TGGGGCTCCT ATGCCATCAC TGTCTTAAAT GATGTGTTTA 4320

AACCTATGTT GTTATAATAA TGATCTATAT GTTAAGTTAA AAGGCTTGCA GGTGGTGCAG 4380

AAAGAAGTCT GGTCACAACT GGCTACAGTG AACAAGCTGG GTACCCCAAG GACATCTTAC 4440

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CGCAAGGGCT GCTAAAGGAA GCGGAACACG TAGAAAGCCA GTCCGCAGAA ACGGTGCTGA 4920

CCCCGGATGA ATGTCAGCTA CTGGGCTATC TGGACAAGGG AAAACGCAAG CGCAAAGAGA 4980
AAGCAGGTAG CTTGCAGTGG GCTTACATGG CGATAGCTAG ACTGGGCGGT TTTATGGACA 5040

GCAAGCGAAC CGGAATTGCC AGCTGGGGCG CCCTCTGGTA AGGTTGGGAA GCCCTGCAAA 5100

GTAAACTGGA TGGCTTTCTT GCCGCCAAGG ATCTGATGGC GCAGGGGATC AAGATCTGAT 5160

CAAGAGACAG GATGAGGATC GTTTCGCATG ATTGAACAAG ATGGATTGCA CGCAGGTTCT 5220

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GTCGGGTTTC GCCACCTCTG ACTTGAGCGT CGATTTTTGT GATGCTCGTC AGGGGGGCGG 6660

AGCCTATGGA AAAACGCCAG CAACGCCGAG ATGCGCCGCC TCGAGTACAC CTGCGTCATG 6720

CTGAGACCCT CAAGCCTCAC TAAAAGGGTC CCTGCCTAGT TCTGTTTACT AATCTGCCTT 6780

ATTCTGTTTT TGTTCCCATG TTAAAGATAG AGTAAATGCA GTATTCTCCA CATAGAGATA 6840

TAGACTTCTG AAATTCTAAG ATTAGAATTA TTTACAAGAA GAAGTGGGGA A 6891

(2) INFORMATION FOR SEQ ID NO:17:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6321 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:17:

TGAAGAATAA AAAATTACTG GCCTCTTGTG AGAACATGAA CTTTCACCTC GGAGCCCACC 60

CCCTCCCATC TGGAAAACAT ACTTGAGAAA AACATTTTCT GGAACAACCA CAGAATGTTT 120

CAACAGGCCA GATGTATTGC CAAACACAGG ATATGACTCT TTGGTTGAGT AAATTTGTGG 180

TTGTTAAACT TCCCCTATTC CCTCCCCATT CCCCCTCCCA GTTTGTGGTT TTTTCCTTTA 240

AAAGCTTGTG AAAAATTTGA GTCGTCGTCG AGACTCCTCT ACCCTGTGCA AAGGTGTATG 300

AGTTTCGACC CCAGAGCTCT GTGTGCTTTC TGTTGCTGCT TTATTTCGAC CCCAGAGCTC 360

TGGTCTGTGT GCTTTCATGT CGCTGCTTTA TTAAATCTTA CCTTCTACAT TTTATGTATG 420

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CGCCTGGTGG ACCCCTTTGA AGGCCAAGAG ACCATTTGGG GTTGCGAGAT CGTGGGTTCG 900

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CATTCCTAGG GGTCTTTCCC CTCTCGCCAA AGGAATGCAA GGTCTGTTGA ATGTCGTGAA 1740

GGAAGCAGTT CCTCTGGAAG CTTCTTGAAG ACAAACAACG TCTGTAGCGA CCCTTTGCAG 1800

GCAGCGGAAC CCCCCACCTG GCGACAGGTG CCTCTGCGGC CAAAAGCCAC GTGTATAAGA 1860

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CCATTGTATG GGATCTGATC TGGGGCCTCG GTGCACATGC TTTACATGTG TTTAGTCGAG 2040

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ATACGGGATC CACCGGTCGC CACCATGGGT AAAGGAGAAG AACTTTTCAC AGGAGTTGTC 2160

CCAATTCTTG TTGAATTAGA TGGTGATGTT AATGGGCACA AATTTTCTGT CAGTGGAGAG 2220

GGTGAAGGTG ATGCAACATA CGGAAAACTT ACCCTTAAAT TTATTTGCAC TACTGGAAAA 2280

CTACCTGTTC CATGGCCAAC ACTTGTCACT ACTTTCACTT ATGGTGTTCA ATGCTTTTCA 2340

AGATACCCAG ATCATATGAA ACGGCATGAC TTTTTCAAGA GTGCCATGCC CGAAGGTTAT 2400

GTACAGGAAA GAACTATATT TTTCAAAGAT GACGGGAACT ACAAGACACG TGCTGAAGTC 2460

AAGTTTGAAG GTGATACCCT TGTTAATAGA ATCGAGTTAA AAGGTATTGA TTTTAAAGAA 2520

GATGGAAACA TTCTTGGACA CAAATTGGAA TACAACTATA ACTCACACAA TGTATACATC 2580

ATGGCAGACA AACAAAAGAA TGGAACCAAA GTTAACTTCA AAATTAGACA CAACATTGAA 2640

GATGGAAGCG TTCAACTAGC AGACCATTAT CAACAAAATA CTCCAATTGG CGATGGCCCT 2700

GTCCTTTTAC CAGACAACCA TTACCTGTCC ACACAATCTG CCCTTTCGAA AGATCCCAAC 2760

GAAAAGAGAG ACCACATGGT CCTTCTTGAG TTTGTAACAG CTGCTGGGAT TACACATGGC 2820

ATGGATGAAC TATACAAGTC CGGATCTAGA TAACTGTATC GATGGATCCG AAGGCGGGGA 2880

CAGCAGTGCA GTGGTGGACA GAAAGCAAGT GATCTAGGCC AGCAGCCTCC CTAAAGGGAC 2940

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AGGTAAGTCA GGGTGTGGCC AAGTATTTAG AGGTCAAATG AAAATTCCAT TGTGTGTACA 3540
GACCTCAGAG CTCAGGAAAG ATAAAAAAGA ATAAATAAAA CTCTAAACAG ACCTTGACAA 3600

AATTAATCCT AGAGACTGGC ACAGACTTAC TTGGTACTCC TTCCCCTTGC CCTATTTAGA 3660

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GACGTTGTCA CTGAAGCGGG AAGGGACTGG CTGCTATTGG GCGAAGTGCC GGGGCAGGAT 4920

CTCCTGTCAT CTCACCTTGC TCCTGCCGAG AAAGTATCCA TCATGGCTGA TGCAATGCGG 4980

CGGCTGCATA CGCTTGATCC GGCTACCTGC CCATTCGACC ACCAAGCGAA ACATCGCATC 5040

GAGCGAGCAC GTACTCGGAT GGAAGCCGGT CTTGTCGATC AGGATGATCT GGACGAAGAG 5100

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CATCACGAGA TTTCGATTCC ACCGCCGCCT TCTATGAAAG GTTGGGCTTC GGAATCGTTT 5520
TCCGGGACGG AATTCGTAAT CTGCTGCTTG CAAACAAAAA AACCACCGCT ACCAGCGGTG 5580

GTTTGTTTGC CGGATCAAGA GCTACCAACT CTTTTTCCGA AGGTAACTGG CTTCAGCAGA 5640

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CCTGCCTAGT TCTGTTTACT AATCTGCCTT ATTCTGTTTT TGTTCCCATG TTAAAGATAG 6240

AGTAAATGCA GTATTCTCCA CATAGAGATA TAGACTTCTG AAATTCTAAG ATTAGAATTA 6300

TTTACAAGAA GAAGTGGGGA A 6321

(2) INFORMATION FOR SEQ ID NO:18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5754 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:

TGAAGAATAA AAAATTACTG GCCTCTTGTG AGAACATGAA CTTTCACCTC GGAGCCCACC 60

CCCTCCCATC TGGAAAACAT ACTTGAGAAA AACATTTTCT GGAACAACCA CAGAATGTTT 120

CAACAGGCCA GATGTATTGC CAAACACAGG ATATGACTCT TTGGTTGAGT AAATTTGTGG 180

TTGTTAAACT TCCCCTATTC CCTCCCCATT CCCCCTCCCA GTTTGTGGTT TTTTCCTTTA 240

AAAGCTTGTG AAAAATTTGA GTCGTCGTCG AGACTCCTCT ACCCTGTGCA AAGGTGTATG 300

AGTTTCGACC CCAGAGCTCT GTGTGCTTTC TGTTGCTGCT TTATTTCGAC CCCAGAGCTC 360

TGGTCTGTGT GCTTTCATGT CGCTGCTTTA TTAAATCTTA CCTTCTACAT TTTATGTATG 420

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ACCTCGTGTT TTGTTGCGAG ATCGTGGGTT CGAGTCCCAC CTCGCGTCTG GTCACGGGAT 1080

CGTGGGTTCG AGTCCCACCT CGTGCAGAGG GTCTCAATTG GCCGGCCTTA GAGAGGCCAT 1140

CTGATTCTTC TGGTTTCTCT TTTTGTCTTA GTCTCGTGTC CGCTCTTGTT GTGACTACTG 1200

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GTTAATGGGC ACAAATTTTC TGTCAGTGGA GAGGGTGAAG GTGATGCAAC ATACGGAAAA 1680

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AGAATCGAGT TAAAAGGTAT TGATTTTAAA GAAGATGGAA ACATTCTTGG ACACAAATTG 1980

GAATACAACT ATAACTCACA CAATGTATAC ATCATGGCAG ACAAACAAAA GAATGGAACC 2040

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CAGAAAGAAG TCTGGTCACA ACTGGCTACA GTGAACAAGC TGGGTACCCC AAGGACATCT 3300

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GATCAAGAGA CAGGATGAGG ATCGTTTCGC ATGATTGAAC AAGATGGATT GCACGCAGGT 4080

TCTCCGGCCG CTTGGGTGGA GAGGCTATTC GGCTATGACT GGGCACAACA GACAATCGGC 4140

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GCCTGCTTGC CGAATATCAT GGTGGAAAAT GGCCGCTTTT CTGGATTCAT CGACTGTGGC 4680

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ATATAGACTT CTGAAATTCT AAGATTAGAA TTATTTACAA GAAGAAGTGG GGAA 5754

(2) INFORMATION FOR SEQ ID NO:19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5754 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:

TGAAGAATAA AAAATTACTG GCCTCTTGTG AGAACATGAA CTTTCACCTC GGAGCCCACC 60

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CAACAGGCCA GATGTATTGC CAAACACAGG ATATGACTCT TTGGTTGAGT AAATTTGTGG 180

TTGTTAAACT TCCCCTATTC CCTCCCCATT CCCCCTCCCA GTTTGTGGTT TTTTCCTTTA 240

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AGTTTCGACC CCAGAGCTCT GTGTGCTTTC TGTTGCTGCT TTATTTCGAC CCCAGAGCTC 360

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GGTCTTGTCG ATCAGGATGA TCTGGACGAA GAGCATCAGG GGCTCGCGCC AGCCGAACTG 4560

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GACTCAAGAC GATAGTTACC GGATAAGGCG CAGCGGTCGG GCTGAACGGG GGGTTCGTGC 5280

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ATATAGACTT CTGAAATTCT AAGATTAGAA TTATTTACAA GAAGAAGTGG GGAA 5754

(2) INFORMATION FOR SEQ ID NO:20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4958 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:

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AAAAGGGTCC CTGCCTAGTT CTGTTTACTA ATCTGCCTTA TTCTGTTTTT GTTCCCATGT 3360

TAAAGATAGA GTAAATGCAG TATTCTCCAC ATAGAGATAT AGACTTCTGA AATTCTAAGA 3420

TTAGAATTAT TTACAAGAAG AAGTGGGGAA TGAAGAATAA AAAATTACTG GCCTCTTGTG 3480

AGAACATGAA CTTTCACCTC GGAGCCCACC CCCTCCCATC TGGAAAACAT ACTTGAGAAA 3540

AACATTTTCT GGAACAACCA CAGAATGTTT CAACAGGCCA GATGTATTGC CAAACACAGG 3600

ATATGACTCT TTGGTTGAGT AAATTTGTGG TTGTTAAACT TCCCCTATTC CCTCCCCATT 3660

CCCCCTCCCA GTTTGTGGTT TTTTCCTTTA AAAGCTTGTG AAAAATTTGA GTCGTCGTCG 3720

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TGTTGCTGCT TTATTTCGAC CCCAGAGCTC TGGTCTGTGT GCTTTCATGT CGCTGCTTTA 3840

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CCCGGGACTT GAGTGTCTGA GTGAGGGTCT TCCCTCGAGG GTCTTTCATT TGGTACATGG 3960

GCCGGGAATT CGAGAATCTT TCATTTGGTG CATTGGCCGG GAATTCGAAA ATCTTTCATT 4020
TGGTGCATTG GCCGGGAAAC AGCGCGACCA CCCAGAGGTC CTAGACCCAC TTAGAGGTAA 4080

GATTCTTTGT TCTGTTTTGG TCTGATGTCT GTGTTCTGAT GTCTGTGTTC TGTTTCTAAG 4140

TCTGGTGCGA TCGCAGTTTC AGTTTTGCGG ACGCTCAGTG AGACCGCGCT CCGAGAGGGA 4200

GTGCGGGGTG GATAAGGATA GACGTGTCCA GGTGTCCACC GTCCGTTCGC CCTGGGAGAC 4260

GTCCCAGGAG GAACAGGGGA GGATCAGGGA CGCCTGGTGG ACCCCTTTGA AGGCCAAGAG 4320

ACCATTTGGG GTTGCGAGAT CGTGGGTTCG AGTCCCACCT CGTGCCCAGT TGCGAGATCG 4380

TGGGTTCGAG TCCCACCTCG TGTTTTGTTG CGAGATCGTG GGTTCGAGTC CCACCTCGCG 4440

TCTGGTCACG GGATCGTGGG TTCGAGTCCC ACCTCGTGTT TTGTTGCGAG ATCGTGGGTT 4500

CGAGTCCCAC CTCGCGTCTG GTCACGGGAT CGTGGGTTCG AGTCCCACCT CGTGCAGAGG 4560

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CTCCCCTTTC TCTGACTCTG GTTCTGTCGC TTGGTAATTT TGTTTGTTTA CGTTTGTTTT 4740

TGTGAGTCGT CTATGTTGTC TGTTACTATC TTGTTTTTGT TTGTGGTTTA CGGTTTCTGT 4800

GTGTGTCTTG TGTGTCTCTT TGTGTTCAGA CTTGGACTGA TGACTGACGA CTGTTTTTAA 4860

GTTATGCCTT CTAAAATAAG CCTAAAAATC CTGTCAGATC CCTATGCTGA CCACTTCCTT 4920

TCAGATCAAC AGCTGCCCTT ACGTATCGAT GGATCCGA 4958

(2) INFORMATION FOR SEQ ID NO:21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7080 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:

GAATACAAGC TTGCATGCCT GCAGGTCGAC TCTAGAGGAT CTTGAAGAAT AAAAAATTAC 60

TGGCCTCTTG TGAGAACATG AACTTTCACC TCGGAGCCCA CCCCCTCCCA TCTGGAAAAC 120

ATACTTGAGA AAAACATTTT CTGGAACAAC CACAGAATGT TTCAACAGGC CAGATGTATT 180

GCCAAACACA GGATATGACT CTTTGGTTGA GTAAATTTGT GGTTGTTAAA CTTCCCCTAT 240

TCCCTCCCCA TTCCCCCTCC CAGTTTGTGG TTTTTTCCTT TAAAAGCTTG TGAAAAATTT 300

GAGTCGTCGT CGAGACTCCT CTACCCTGTG CAAAGGTGTA TGAGTTTCGA CCCCAGAGCT 360

CTGTGTGCTT TCTGTTGCTG CTTTATTTCG ACCCCAGAGC TCTGGTCTGT GTGCTTTCAT 420

GTCGCTGCTT TATTAAATCT TACCTTCTAC ATTTTATGTA TGGTCTCAGT GTCTTCTTGG 480

GTACGCGGCT GTCCCGGGAC TTGAGTGTCT GAGTGAGGGT CTTCCCTCGA GGGTCTTTCA 540

TTTGGTACAT GGGCCGGGAA TTCGAGAATC TTTCATTTGG TGCATTGGCC GGGAATTCGA 600

AAATCTTTCA TTTGGTGCAT TGGCCGGGAA ACAGCGCGAC CACCCAGAGG TCCTAGACCC 660

ACTTAGAGGT AAGATTCTTT GTTCTGTTTT GGTCTGATGT CTGTGTTCTG ATGTCTGTGT 720

TCTGTTTCTA AGTCTGGTGC GATCGCAGTT TCAGTTTTGC GGACGCTCAG TGAGACCGCG 780

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GCAGAGGGTC TCAATTGGCC GGCCTTAGAA TTACGGATCT AGCATGATTG AACAAGATGG 1020

ATTGCACGCA GGTTCTCCGG CCGCTTGGGT GGAGAGGCTA TTCGGCTATG ACTGGGCACA 1080

ACAGACAATC GGCTGCTCTG ATGCCGCCGT GTTCCGGCTG TCAGCGCAGG GGCGCCCGGT 1140

TCTTTTTGTC AAGACCGACC TGTCCGGTGC CCTGAATGAA CTGCAGGACG AGGCAGCGCG 1200

GCTATCGTGG CTGGCCACGA CGGGCGTTCC TTGCGCAGCT GTGCTCGACG TTGTCACTGA 1260

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CCTTGCTCCT GCCGAGAAAG TATCCATCAT GGCTGATGCA ATGCGGCGGC TGCATACGCT 1380

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TCGGATGGAA GCCGGTCTTG TCGATCAGGA TGATCTGGAC GAAGAGCATC AGGGGCTCGC 1500

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TTGTCAATTC TATTATTTCA ATACAGAACA ATAGCTTCTA TAACTGAAAT ATATTTGCTA 1980

TTGTATATTA TGATTGTCCC TCGAACCATG AACACTCCTC CAGCTGAATT TCACAATTCC 2040

TCTGTCATCT GCCAGGCCAT TAAGTTATTC ATGGAAGATC TTTGAGGAAC ACTGCAAGTT 2100

CATATCATAA ACACATTTGA AATTGAGTAT TGTTTTGCAT TGTATGGAGC TATGTTTTGC 2160

TGTATCCTCA GAAAAAAAGT TTGTTATAAA GCATTCACAC CCATAAAAAG ATAGATTTAA 2220

ATATTCCAGC TATAGGAAAG AAAGTGCGTC TGCTCTTCAC TCTAGTCTCA GTTGGCTCCT 2280

TCACATGCAT GCTTCTTTAT TTCTCCTATT TTGTCAAGAA AATAATAGGT CACGTCTTGT 2340

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GCTAATTATG TTTTCCATCT CTAAGGTTCC CACATTTTTC TGTTTTCTTA AAGATCCCAT 2520
TATCTGGTTG TAACTGAAGC TCAATGGAAC ATGAGCAATA TTTCCCAGTC TTCTCTCCCA 2580

TCCAACAGTC CTGATGGATT AGCAGAACAG GCAGAAAACA CATTGTTACC CAGAATTAAA 2640

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ATCCCATTAA ATGATTTCTA TGGCGTCAAA GGTCAAACTT CTGAAGGGAA CCTGTGGGTG 2760

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TTATCCAGGC TTTTTGACAA CGCTATGCTC CGCGCCCATC GTCTGCACCA GCTGGCCTTT 3000

GACACCTACC AGGAGTTTGA AGAAGCCTAT ATCCCAAAGG AACAGAAGTA TTCATTCCTG 3060

CAGAACCCCC AGACCTCCCT CTGTTTCTCA GAGTCTATTC CGACACCCTC CAACAGGGAG 3120

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TGGCTGGAGC CCGTGCAGTT CCTCAGGAGT GTCTTCGCCA ACAGCCTGGT GTACGGCGCC 3240

TCTGACAGCA ACGTCTATGA CCTCCTAAAG GACCTAGAGG AAGGCATCCA AACGCTGATG 3300

GGGAGGCTGG AAGATGGCAG CCCCCGGACT GGGCAGATCT TCAAGCAGAC CTACAGCAAG 3360

TTCGACACAA ACTCACACAA CGATGACGCA CTACTCAAGA ACTACGGGCT GCTCTACTGC 3420

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ATTTACAAGA AGAAGTGGGG AATGAAGAAT AAAAAATTAC TGGCCTCTTG TGAGAACATG 3720

AACTTTCACC TCGGAGCCCA CCCCCTCCCA TCTGGAAAAC ATACTTGAGA AAAACATTTT 3780

CTGGAACAAC CACAGAATGT TTCAACAGGC CAGATGTATT GCCAAACACA GGATATGACT 3840

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CAGTTTGTGG TTTTTTCCTT TAAAAGCTTG TGAAAAATTT GAGTCGTCGT CGAGACTCCT 3960

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CTTTATTTCG ACCCCAGAGC TCTGGTCTGT GTGCTTTCAT GTCGCTGCTT TATTAAATCT 4080

TACCTTCTAC ATTTTATGTA TGGTCTCAGT GTCTTCTTGG GTACGCGGCT GTCCCGGGAC 4140

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TACCGAGCTC GAATTCCGGT CTCCCTATAG TGAGTCGTAT TAATTTCGAT AAGCCAGCTG 4320

CATTAATGAA TCGGCCAACG CGCGGGGAGA GGCGGTTTGC GTATTGGGCG CTCTTCCGCT 4380

TCCTCGCTCA CTGACTCGCT GCGCTCGGTC GTTCGGCTGC GGCGAGCGGT ATCAGCTCAC 4440

TCAAAGGCGG TAATACGGTT ATCCACAGAA TCAGGGGATA ACGCAGGAAA GAACATGTGA 4500
GCAAAAGGCC AGCAAAAGGC CAGGAACCGT AAAAAGGCCG CGTTGCTGGC GTTTTTCCAT 4560

AGGCTCCGCC CCCCTGACGA GCATCACAAA AATCGACGCT CAAGTCAGAG GTGGCGAAAC 4620

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TAAAGTATAT ATGAGTAAAC TTGGTCTGAC AGTTACCAAT GCTTAATCAG TGAGGCACCT 5340

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ACTACGATAC GGGAGGGCTT ACCATCTGGC CCCAGTGCTG CAATGATACC GCGAGACCCA 5460

CGCTCACCGG CTCCAGATTT ATCAGCAATA AACCAGCCAG CCGGAAGGGC CGAGCGCAGA 5520

AGTGGTCCTG CAACTTTATC CGCCTCCATC CAGTCTATTA ATTGTTGCCG GGAAGCTAGA 5580

GTAAGTAGTT CGCCAGTTAA TAGTTTGCGC AACGTTGTTG CCATTGCTAC AGGCATCGTG 5640

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CTTTTTCAAT ATTATTGAAG CATTTATCAG GGTTATTGTC TCATGAGCGG ATACATATTT 6240

GAATGTATTT AGAAAAATAA ACAAATAGGG GTTCCGCGCA CATTTCCCCG AAAAGTGCCA 6300

CCTGACGTCT AAGAAACCAT TATTATCATG ACATTAACCT ATAAAAATAG GCGTATCACG 6360

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CCGGAGACGG TCACAGCTTG TCTGTAAGCG GATGCCGGGA GCAGACAAGC CCGTCAGGGC 6480
GCGTCAGCGG GTGTTGGCGG GTGTCGGGGC TGGCTTAACT ATGCGGCATC AGAGCAGATT 6540

GTACTGAGAG TGCACCATAT CGACGCTCTC CCTTATGCGA CTCCTGCATT AGGAAGCAGC 6600

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AACCGCACCT GTGGCGCCGG TGATGCCGGC CACGATGCGT CCGGCGTAGA GGATCTGGCT 6840

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GCGGCTACAA TTAATACATA ACCTTATGTA TCATACACAT ACGATTTAGG TGACACTATA 7080

(2) INFORMATION FOR SEQ ID NO:22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6795 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:

AATGAAAGAC CCCACCTGTA GGTTTGGCAA GCTAGCTTAA GTAACGCCAT TTTGCAAGGC 60

ATGGAAAAAT ACATAACTGA GAATAGAGAA GTTCAGATCA AGGTCAGGAA CAGATGGAAC 120

AGCTGAATAT GGGCCAAACA GGATATCTGT GGTAAGCAGT TCCTGCCCCG GCTCAGGGCC 180

AAGAACAGAT GGAACAGCTG AATATGGGCC AAACAGGATA TCTGTGGTAA GCAGTTCCTG 240

CCCCGGCTCA GGGCCAAGAA CAGATGGTCC CCAGATGCGG TCCAGCCCTC AGCAGTTTCT 300

AGAGAACCAT CAGATGTTTC CAGGGTGCCC CAAGGACCTG AAATGACCCT GTGCCTTATT 360

TGAACTAACC AATCAGTTCG CTTCTCGCTT CTGTTCGCGC GCTTCTGCTC CCCGAGCTCA 420

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CTTGGGAGGG TCTCCTCTGA GTGATTGACT ACCCGTCAGC GGGGGTCTTT CATTTGGGGG 600

CTCGTCCGGG ATCGGGAGAC CCCTGCCCAG GGACCACCGA CCCACCACCG GGAGGTAAGC 660

TGGCCAGCAA CTTATCTGTG TCTGTCCGAT TGTCTAGTGT CTATGACTGA TTTTATGCGC 720

CTGCGTCGGT ACTAGTTAGC TAACTAGCTC TGTATCTGGC GGACCCGTGG TGGAACTGAC 780

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TTCGAGTCCC ACCTCGTGCC CAGTTGCGAG ATCGTGGGTT CGAGTCCCAC CTCGTGTTTT 960

GTTGCGAGAT CGTGGGTTCG AGTCCCACCT CGCGTCTGGT CACGGGATCG TGGGTTCGAG 1020

TCCCACCTCG TGTTTTGTTG CGAGATCGTG GGTTCGAGTC CCACCTCGCG TCTGGTCACG 1080

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CAGACTTGGA CTGATGACTG ACGACTGTTT TTAAGTTATG CCTTCTAAAA TAAGCCTAAA 1440

AATCCTGTCA GATCCCTATG CTGACCACTT CCTTTCAGAT CAACAGCTGC CCTTACTCGA 1500

GCTCAAGCTT CGAATTCTGC AGTCGACGGT ACCGCGGCCG CTAACTAATA GCCCATTCTC 1560

CAAGGTACGT AGCGGGGATC AATTCCGCCC CCCCCCTAAC GTTACTGGCC GAAGCCGCTT 1620

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CCCCCCGAAC CACGGGGACG TGGTTTTCCT TTGAAAAACA CGATACGGGA TCCACCGGTC 2160

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TACGGAAAAC TTACCCTTAA ATTTATTTGC ACTACTGGAA AACTACCTGT TCCATGGCCA 2340

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AAACGGCATG ACTTTTTCAA GAGTGCCATG CCCGAAGGTT ATGTACAGGA AAGAACTATA 2460

TTTTTCAAAG ATGACGGGAA CTACAAGACA CGTGCTGAAG TCAAGTTTGA AGGTGATACC 2520

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CATTACCTGT CCACACAATC TGCCCTTTCG AAAGATCCCA ACGAAAAGAG AGACCACATG 2820

GTCCTTCTTG AGTTTGTAAC AGCTGCTGGG ATTACACATG GCATGGATGA ACTATACAAG 2880
TCCGGATCTA GATAACTGTA TCGATGGATC CGAAGGCGGG GACAGCAGTG CAGTGGTGGA 2940

CAGAAAGCAA GTGATCTAGG CCAGCAGCCT CCCTAAAGGG ACTTCAGCCC ACAAAGCCAA 3000

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GACCCTGTGG AATGTGTGTC AGTTAGGGTG TGGAAAGTCC CCAGGCTCCC CAGCAGGCAG 4020

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GACTGTGGCC GGCTGGGTGT GGCGGACCGC TATCAGGACA TAGCGTTGGC TACCCGTGAT 5340

ATTGCTGAAG AGCTTGGCGG CGAATGGGCT GACCGCTTCC TCGTGCTTTA CGGTATCGCC 5400

GCTCCCGATT CGCAGCGCAT CGCCTTCTAT CGCCTTCTTG ACGAGTTCTT CTGAGCGGGA 5460

CTCTGGGGTT CGAAATGACC GACCAAGCGA CGCCCAACCT GCCATCACGA GATTTCGATT 5520

CCACCGCCGC CTTCTATGAA AGGTTGGGCT TCGGAATCGT TTTCCGGGAC GGAATTCGTA 5580

ATCTGCTGCT TGCAAACAAA AAAACCACCG CTACCAGCGG TGGTTTGTTT GCCGGATCAA 5640

GAGCTACCAA CTCTTTTTCC GAAGGTAACT GGCTTCAGCA GAGCGCAGAT ACCAAATACT 5700

GTCCTTCTAG TGTAGCCGTA GTTAGGCCAC CACTTCAAGA ACTCTGTAGC ACCGCCTACA 5760

TACCTCGCTC TGCTAATCCT GTTACCAGTG GCTGCTGCCA GTGGCGATAA GTCGTGTCTT 5820

ACCGGGTTGG ACTCAAGACG ATAGTTACCG GATAAGGCGC AGCGGTCGGG CTGAACGGGG 5880

GGTTCGTGCA CACAGCCCAG CTTGGAGCGA ACGACCTACA CCGAACTGAG ATACCTACAG 5940

CGTGAGCATT GAGAAAGCGC CACGCTTCCC GAAGGGAGAA AGGCGGACAG GTATCCGGTA 6000

AGCGGCAGGG TCGGAACAGG AGAGCGCACG AGGGAGCTTC CAGGGGGAAA CGCCTGGTAT 6060

CTTTATAGTC CTGTCGGGTT TCGCCACCTC TGACTTGAGC GTCGATTTTT GTGATGCTCG 6120

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CCTGGCCCTA TTATTGGGTG GACTAACCAT GGGGGGAATT GCCGCTGGAA TAGGAACAGG 6240

GACTACTGCT CTAATGGCCA CTCAGCAATT CCAGCAGCTC CAAGCCGCAG TACAGGATGA 6300

TCTCAGGGAG GTTGAAAAAT CAATCTCTAA CCTAGAAAAG TCTCTCACTT CCCTGTCTGA 6360

AGTTGTCCTA CAGAATCGAA GGGGCCTAGA CTTGTTATTT CTAAAAGAAG GAGGGCTGTG 6420

TGCTGCTCTA AAAGAAGAAT GTTGCTTCTA TGCGGACCAC ACAGGACTAG TGAGAGACAG 6480

CATGGCCAAA TTGAGAGAGA GGCTTAATCA GAGACAGAAA CTGTTTGAGT CAACTCAAGG 6540

ATGGTTTGAG GGACTGTTTA ACAGATCCCC TTGGTTTACC ACCTTGATAT CTACCATTAT 6600

GGGACCCCTC ATTGTACTCC TAATGATTTT GCTCTTCGGA CCCTGCATTC TTAATCGATT 6660

AGTCCAATTT GTTAAAGACA GGATATCAGT GGTCCAGGCT CTAGTTTTGA CTCAACAATA 6720

TCACCAGCTG AAGCCTATAG AGTACGAGCC ATAGATAAAA TAAAAGATTT TATTTAGTCT 6780

CCAGAAAAAG GGGGG 6795

(2) INFORMATION FOR SEQ ID NO:23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9093 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:

AATGAAAGAC CCCACCTGTA GGTTTGGCAA GCTAGCTTAA GTAACGCCAT TTTGCAAGGC 60

ATGGAAAAAT ACATAACTGA GAATAGAGAA GTTCAGATCA AGGTCAGGAA CAGATGGAAC 120

AGCTGAATAT GGGCCAAACA GGATATCTGT GGTAAGCAGT TCCTGCCCCG GCTCAGGGCC 180

AAGAACAGAT GGAACAGCTG AATATGGGCC AAACAGGATA TCTGTGGTAA GCAGTTCCTG 240

CCCCGGCTCA GGGCCAAGAA CAGATGGTCC CCAGATGCGG TCCAGCCCTC AGCAGTTTCT 300

AGAGAACCAT CAGATGTTTC CAGGGTGCCC CAAGGACCTG AAATGACCCT GTGCCTTATT 360

TGAACTAACC AATCAGTTCG CTTCTCGCTT CTGTTCGCGC GCTTCTGCTC CCCGAGCTCA 420

ATAAAAGAGC CCACAACCCC TCACTCGGGG CGCCAGTCCT CCGATTGACT GAGTCGCCCG 480

GGTACCCGTG TATCCAATAA ACCCTCTTGC AGTTGCATCC GACTTGTGGT CTCGCTGTTC 540

CTTGGGAGGG TCTCCTCTGA GTGATTGACT ACCCGTCAGC GGGGGTCTTT CATTTGGGGG 600

CTCGTCCGGG ATCGGGAGAC CCCTGCCCAG GGACCACCGA CCCACCACCG GGAGGTAAGC 660

TGGCCAGCAA CTTATCTGTG TCTGTCCGAT TGTCTAGTGT CTATGACTGA TTTTATGCGC 720

CTGCGTCGGT ACTAGTTAGC TAACTAGCTC TGTATCTGGC GGACCCGTGG TGGAACTGAC 780

GAGTTCGGAA CACCCGGCCG CAACCCTGGG AGACGTCCCA GGAGGAACAG GGGAGGATCA 840

GGGACGCCTG GTGGACCCCT TTGAAGGCCA AGAGACCATT TGGGGTTGCG AGATCGTGGG 900

TTCGAGTCCC ACCTCGTGCC CAGTTGCGAG ATCGTGGGTT CGAGTCCCAC CTCGTGTTTT 960

GTTGCGAGAT CGTGGGTTCG AGTCCCACCT CGCGTCTGGT CACGGGATCG TGGGTTCGAG 1020

TCCCACCTCG TGTTTTGTTG CGAGATCGTG GGTTCGAGTC CCACCTCGCG TCTGGTCACG 1080

GGATCGTGGG TTCGAGTCCC ACCTCGTGCA GAGGGTCTCA ATTGGCCGGC CTTAGAGAGG 1140

CCATCTGATT CTTCTGGTTT CTCTTTTTGT CTTAGTCTCG TGTCCGCTCT TGTTGTGACT 1200

ACTGTTTTTC TAAAAATGGG ACAATCTGTG TCCACTCCCC TTTCTCTGAC TCTGGTTCTG 1260

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CAGACTTGGA CTGATGACTG ACGACTGTTT TTAAGTTATG CCTTCTAAAA TAAGCCTAAA 1440

AATCCTGTCA GATCCCTATG CTGACCACTT CCTTTCAGAT CAACAGCTGC CCTTACGTAT 1500

CGATGGATCC CTCGACTAAC TAATAGCCCA TTCTCCAAGG TCGAGCGGGA TCAATTCCGC 1560

CCCCCCCCTA ACGTTACTGG CCGAAGCCGC TTGGAATAAG GCCGGTGTGC GTTTGTCTAT 1620

ATGTTATTTT CCACCATATT GCCGTCTTTT GGCAATGTGA GGGCCCGGAA ACCTGGCCCT 1680

GTCTTCTTGA CGAGCATTCC TAGGGGTCTT TCCCCTCTCG CCAAAGGAAT GCAAGGTCTG 1740

TTGAATGTCG TGAAGGAAGC AGTTCCTCTG GAAGCTTCTT GAAGACAAAC AACGTCTGTA 1800

GCGACCCTTT GCAGGCAGCG GAACCCCCCA CCTGGCGACA GGTGCCTCTG CGGCCAAAAG 1860

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GCCCAGAAGG TACCCCATTG TATGGGATCT GATCTGGGGC CTCGGTGCAC ATGCTTTACA 2040

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GGCGTAATAG CGAAGAGGCC CGCACCGATC GCCCTTCCCA ACAGTTGCGC AGCCTGAATG 2280

GCGAATGGCG CTTTGCCTGG TTTCCGGCAC CAGAAGCGGT GCCGGAAAGC TGGCTGGAGT 2340

GCGATCTTCC TGAGGCCGAT ACTGTCGTCG TCCCCTCAAA CTGGCAGATG CACGGTTACG 2400

ATGCGCCCAT CTACACCAAC GTAACCTATC CCATTACGGT CAATCCGCCG TTTGTTCCCA 2460

CGGAGAATCC GACGGGTTGT TACTCGCTCA CATTTAATGT TGATGAAAGC TGGCTACAGG 2520

AAGGCCAGAC GCGAATTATT TTTGATGGCG TTAACTCGGC GTTTCATCTG TGGTGCAACG 2580

GGCGCTGGGT CGGTTACGGC CAGGACAGTC GTTTGCCGTC TGAATTTGAC CTGAGCGCAT 2640

TTTTACGCGC CGGAGAAAAC CGCCTCGCGG TGATGGTGCT GCGTTGGAGT GACGGCAGTT 2700

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ATAAACCGAC TACACAAATC AGCGATTTCC ATGTTGCCAC TCGCTTTAAT GATGATTTCA 2820

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TGAGCGAACG CGTAACGCGA ATGGTGCAGC GCGATCGTAA TCACCCGAGT GTGATCATCT 3480
GGTCGCTGGG GAATGAATCA GGCCACGGCG CTAATCACGA CGCGCTGTAT CGCTGGATCA 3540

AATCTGTCGA TCCTTCCCGC CCGGTGCAGT ATGAAGGCGG CGGAGCCGAC ACCACGGCCA 3600

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CGAACGATCG CCAGTTCTGT ATGAACGGTC TGGTCTTTGC CGACCGCACG CCGCATCCAG 3960

CGCTGACGGA AGCAAAACAC CAGCAGCAGT TTTTCCAGTT CCGTTTATCC GGGCAAACCA 4020

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ACCAGGCCGA AGCAGCGTTG TTGCAGTGCA CGGCAGATAC ACTTGCTGAT GCGGTGCTGA 4620

TTACGACCGC TCACGCGTGG CAGCATCAGG GGAAAACCTT ATTTATCAGC CGGAAAACCT 4680

ACCGGATTGA TGGTAGTGGT CAAATGGCGA TTACCGTTGA TGTTGAAGTG GCGAGCGATA 4740

CACCGCATCC GGCGCGGATT GGCCTGAACT GCCAGCTGGC GCAGGTAGCA GAGCGGGTAA 4800

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AGTTCAACAT CAGCCGCTAC AGTCAACAGC AACTGATGGA AACCAGCCAT CGCCATCTGC 5040

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CAAATCTAAC CGCCCAGGCA TCCTAAAGAG CAATGATCCT GACAGTCTGA AGACTATCAA 5520

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CGGCTGCATA CGCTTGATCC GGCTACCTGC CCATTCGACC ACCAAGCGAA ACATCGCATC 7380

GAGCGAGCAC GTACTCGGAT GGAAGCCGGT CTTGTCGATC AGGATGATCT GGACGAAGAG 7440
CATCAGGGGC TCGCGCCAGC CGAACTGTTC GCCAGGCTCA AGGCGCGCAT GCCCGACGGC 7500

GAGGATCTCG TCGTGACCCA TGGCGATGCC TGCTTGCCGA ATATCATGGT GGAAAATGGC 7560

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CGCTGGAATA GGAACAGGGA CTACTGCTCT AATGGCCACT CAGCAATTCC AGCAGCTCCA 8580

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AAAGATTTTA TTTAGTCTCC AGAAAAAGGG GGG 9093

(2) INFORMATION FOR SEQ ID NO:24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:

GACTAACCTT GATTCCCTGG AGGCGGGGGT CTTTCATTTG GGGGCT 46

(2) INFORMATION FOR SEQ ID NO:25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4834 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:

TGAAGAATAA AAAATTACTG GCCTCTTGTG AGAACATGAA CTTTCACCTC GGAGCCCACC 60

CCCTCCCATC TGGAAAACAT ACTTGAGAAA AACATTTTCT GGAACAACCA CAGAATGTTT 120

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TTGTTAAACT TCCCCTATTC CCTCCCCATT CCCCCTCCCA GTTTGTGGTT TTTTCCTTTA 240

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AGTTTCGACC CCAGAGCTCT GTGTGCTTTC TGTTGCTGCT TTATTTCGAC CCCAGAGCTC 360

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CAAGTTATAG ACAAATTAAG ACTGGTAAAA AAAACCCTGT ATAAAATAGT AAAAACTGAA 3420

AAAAGAAAAC TAGTCCTCTC ATGAGAAGAC AGACCTGACA TCTACTGAAA AATAGACTTT 3480

ACTGGAAAAA ATATGTGTAT GAATACCTTC TAGTTTTTGT GAACGTTCTC AAGATGGATA 3540

AAAGCTTTTC CTTGTAAAAC GAGACTGATC AGATAGTCAT CAAGAAGATT GTTAAAGAAA 3600

ATTTTCCAAG GTTCGGAGTG CCAAAAGCAA TAGTGTCAGA TAATGGTCCT GCCTTTGTTG 3660

CCCAGGTAAG TCAGGGTGTG GCCAAGTATT TAGAGGTCAA ATGAAAATTC CATTGTGTGT 3720

ACAGACCTCA GAGCTCAGGA AAGATAAAAA AGAATAAATA AAACTCTAAA CAGACCTTGA 3780

CAAAATTAAT CCTAGAGACT GGCACAGACT TACTTGGTAC TCCTTCCCCT TGCCCTATTT 3840

AGAACTGAGA ATACTCCCTC TTGATTCGGT TTTACTCTTT TTAAGATCCT TTATGGGGCT 3900

CCTATGCCAT CACTGTCTTA AATGATGTGT TTAAACCTAT GTTGTTATAA TAATGATCTA 3960

TATGTTAAGT TAAAAGGCTT GCAGGTGGTG CAGAAAGAAG TCTGGTCACA ACTGGCTACA 4020

GTGAACAAGC TGGGTACCCC AAGGACATCT TACCAGTTCC AGCCAGAGAT CTGATCTACG 4080

TACACCTGCG TCATGCTGAG ACCCTCAAGC CTCACTAAAA GGGTCCCTGC CTAGTTCTGT 4140

TTACTAATCT GCCTTATTCT GTTTTTGTTC CCATGTTAAA GATAGAGTAA ATGCAGTATT 4200

CTCCACATAG AGATATAGAC TTCTGAAATT CTAAGATTAG AATTATTTAC AAGAAGAAGT 4260

GGGGAATGAA GAATAAAAAA TTACTGGCCT CTTGTGAGAA CATGAACTTT CACCTCGGAG 4320

CCCACCCCCT CCCATCTGGA AAACATACTT GAGAAAAACA TTTTCTGGAA CAACCACAGA 4380

ATGTTTCAAC AGGCCAGATG TATTGCCAAA CACAGGATAT GACTCTTTGG TTGAGTAAAT 4440

TTGTGGTTGT TAAACTTCCC CTATTCCCTC CCCATTCCCC CTCCCAGTTT GTGGTTTTTT 4500

CCTTTAAAAG CTTGTGAAAA ATTTGAGTCG TCGTCGAGAC TCCTCTACCC TGTGCAAAGG 4560

TGTATGAGTT TCGACCCCAG AGCTCTGTGT GCTTTCTGTT GCTGCTTTAT TTCGACCCCA 4620

GAGCTCTGGT CTGTGTGCTT TCATGTCGCT GCTTTATTAA ATCTTACCTT CTACATTTTA 4680

TGTATGGTCT CAGTGTCTTC TTGGGTACGC GGCTGTCCCG GGACTTGAGT GTCTGAGTGA 4740

GGGTCTTCCC TCGAGGGTCT TTCATTTGGT ACATGGGCCG GGAATTCGAG AATCTTTCAT 4800

TTGGTGCATT GGCCGGGAAT TCGAAAATCT TTCA 4834

(2) INFORMATION FOR SEQ ID NO:26:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 4518 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:

CACCTGACGC GCCCTGTAGC GGCGCATTAA GCGCGGCGGG TGTGGTGGTT ACGCGCAGCG 60

TGACCGCTAC ACTTGCCAGC GCCCTAGCGC CCGCTCCTTT CGCTTTCTTC CCTTCCTTTC 120

TCGCCACGTT CGCCGGCTTT CCCCGTCAAG CTCTAAATCG GGGGCTCCCT TTAGGGTTCC 180

GATTTAGTGC TTTACGGCAC CTCGACCCCA AAAAACTTGA TTAGGGTGAT GGTTCACGTA 240

GTGGGCCATC GCCCTGATAG ACGGTTTTTC GCCCTTTGAC GTTGGAGTCC ACGTTCTTTA 300

ATAGTGGACT CTTGTTCCAA ACTGGAACAA CACTCAACCC TATCTCGGTC TATTCTTTTG 360

ATTTATAAGG GATTTTGCCG ATTTCGGCCT ATTGGTTAAA AAATGAGCTG ATTTAACAAA 420

AATTTAACGC GAATTTTAAC AAAATATTAA CGCTTACAAT TTACGCGTTA AGATACATTG 480

ATGAGTTTGG ACAAACCACA ACTAGAATGC AGTGAAAAAA ATGCTTTATT TGTGAAATTT 540

GTGATGCTAT TGCTTTATTT GTAACCATTA TAAGCTGCAA TAAACAAGTT AACAACAACA 600

ATTGCATTCA TTTTATGTTT CAGGTTCAGG GGGAGGTGTG GGAGGTTTTT TAAAGCAAGT 660

AAAACCTCTA CAAATGTGGT ATGGCTGATT ATGATCATGA ACAGACTGTG AGGACTGAGG 720

GGCCTGAAAT GAGCCTTGGG ACTGTGAATC TAAAATACAC AAACAATTAG AATCAGTAGT 780

TTAACACATT ATACACTTAA AAATTGGATC TCCATTCGCC ATTCAGGCTG CGCAACTGTT 840

GGGAAGGGCG ATCGGTGCGG GCCTCTTCGC TATTACGCCA GCTGGCGAAA GGGGGATGTG 900

CTGCAAGGCG ATTAAGTTGG GTAACGCCAG GGTTTTCCCA GTCACGACGT TGTAAAACGA 960

CGGCCAGTGA ATTGTAATAC GACTCACTAT AGGGCGAATT GGGTACACTT ACCTGGTACC 1020

CCACCCGGGT GGAAAATCGA TGGGCCCGCG GCCGCTCTAG AAGTACTCTC GAGAAGCTTT 1080

TTGAATTCTT TGGATCCACT AGTGTCGACC TGCAGGCGCG CGAGCTCCAG CTTTTGTTCC 1140

CTTTAGTGAG GGTTAATTTC GAGCTTGGCG TAATCAAGGT CATAGCTGTT TCCTGTGTGA 1200

AATTGTTATC CGCTCACAAT TCCACACAAT ATACGAGCCG GAAGTATAAA GTGTAAAGCC 1260

TGGGGTGCCT AATGAGTGAG CTAACTCACA GTAATTGCGG CTAGCGGATC TGACGGTTCA 1320

CTAAACCAGC TCTGCTTATA TAGACCTCCC ACCGTACACG CCTACCGCCC ATTTGCGTCA 1380

ATGGGGCGGA GTTGTTACGA CATTTTGGAA AGTCCCGTTG ATTTTGGTGC CAAAACAAAC 1440

TCCCATTGAC GTCAATGGGG TGGAGACTTG GAAATCCCCG TGAGTCAAAC CGCTATCCAC 1500

GCCCATTGAT GTACTGCCAA AACCGCATCA CCATGGTAAT AGCGATGACT AATACGTAGA 1560

TGTACTGCCA AGTAGGAAAG TCCCATAAGG TCATGTACTG GGCATAATGC CAGGCGGGCC 1620

ATTTACCGTC ATTGACGTCA ATAGGGGGCG TACTTGGCAT ATGATACACT TGATGTACTG 1680

CCAAGTGGGC AGTTTACCGT AAATACTCCA CCCATTGACG TCAATGGAAA GTCCCTATTG 1740

GCGTTACTAT GGGAACATAC GTCATTATTG ACGTCAATGG GCGGGGGTCG TTGGGCGGTC 1800

AGCCAGGCGG GCCATTTACC GTAAGTTATG TAACGCGGAA CTCCATATAT GGGCTATGAA 1860

CTAATGACCC CGTAATTGAT TACTATTAAT AACTAATGCA TGGCGGTAAT ACGGTTATCC 1920
ACAGAATCAG GGGATAACGC AGGAAAGAAC ATGTGAGCAA AAGGCCAGCA AAAGGCCAGG 1980

AACCGTAAAA AGGCCGCGTT GCTGGCGTTT TTCCATAGGC TCCGCCCCCC TGACGAGCAT 2040

CACAAAAATC GACGCTCAAG TCAGAGGTGG CGAAACCCGA CAGGACTATA AAGATACCAG 2100

GCGTTTCCCC CTGGAAGCTC CCTCGTGCGC TCTCCTGTTC CGACCCTGCC GCTTACCGGA 2160

TACCTGTCCG CCTTTCTCCC TTCGGGAAGC GTGGCGCTTT CTCATAGCTC ACGCTGTAGG 2220

TATCTCAGTT CGGTGTAGGT CGTTCGCTCC AAGCTGGGCT GTGTGCACGA ACCCCCCGTT 2280

CAGCCCGACC GCTGCGCCTT ATCCGGTAAC TATCGTCTTG AGTCCAACCC GGTAAGACAC 2340

GACTTATCGC CACTGGCAGC AGCCACTGGT AACAGGATTA GCAGAGCGAG GTATGTAGGC 2400

GGTGCTACAG AGTTCTTGAA GTGGTGGCCT AACTACGGCT ACACTAGAAG GACAGTATTT 2460

GGTATCTGCG CTCTGCTGAA GCCAGTTACC TTCGGAAAAA GAGTTGGTAG CTCTTGATCC 2520

GGCAAACAAA CCACCGCTGG TAGCGGTGGT TTTTTTGTTT GCAAGCAGCA GATTACGCGC 2580

AGAAAAAAAG GATCTCAAGA AGATCCTTTG ATCTTTTCTA CGGGGTCTGA CGCTCAGTGG 2640

AACGAAAACT CACGTTAAGG GATTTTGGTC ATGAGATTAT CAAAAAGGAT CTTCACCTAG 2700

ATCCTTTTAA ATTAAAAATG AAGTTTTAAA TCAATCTAAA GTATATATGA GTAACCTGAG 2760

GCTATGGCAG GGCCTGCCGC CCCGACGTTG GCTGCGAGCC CTGGGCCTTC ACCCGAACTT 2820

GGGGGGTGGG GTGGGGAAAA GGAAGAAACG CGGGCGTATT GGCCCCAATG GGGTCTCGGT 2880

GGGGTATCGA CAGAGTGCCA GCCCTGGGAC CGAACCCCGC GTTTATGAAC AAACGACCCA 2940

ACACCGTGCG TTTTATTCTG TCTTTTTATT GCCGTCATAG CGCGGGTTCC TTCCGGTATT 3000

GTCTCCTTCC GTGTTTCAGT TAGCCTCCCC CTAGGGTGGG CGAAGAACTC CAGCATGAGA 3060

TCCCCGCGCT GGAGGATCAT CCAGCCGGCG TCCCGGAAAA CGATTCCGAA GCCCAACCTT 3120

TCATAGAAGG CGGCGGTGGA ATCGAAATCT CGTGATGGCA GGTTGGGCGT CGCTTGGTCG 3180

GTCATTTCGA ACCCCAGAGT CCCGCTCAGA AGAACTCGTC AAGAAGGCGA TAGAAGGCGA 3240

TGCGCTGCGA ATCGGGAGCG GCGATACCGT AAAGCACGAG GAAGCGGTCA GCCCATTCGC 3300

CGCCAAGCTC TTCAGCAATA TCACGGGTAG CCAACGCTAT GTCCTGATAG CGGTCCGCCA 3360

CACCCAGCCG GCCACAGTCG ATGAATCCAG AAAAGCGGCC ATTTTCCACC ATGATATTCG 3420

GCAAGCAGGC ATCGCCATGG GTCACGACGA GATCCTCGCC GTCGGGCATG CTCGCCTTGA 3480

GCCTGGCGAA CAGTTCGGCT GGCGCGAGCC CCTGATGCTC TTCGTCCAGA TCATCCTGAT 3540

CGACAAGACC GGCTTCCATC CGAGTACGTG CTCGCTCGAT GCGATGTTTC GCTTGGTGGT 3600

CGAATGGGCA GGTAGCCGGA TCAAGCGTAT GCAGCCGCCG CATTGCATCA GCCATGATGG 3660

ATACTTTCTC GGCAGGAGCA AGGTGAGATG ACAGGAGATC CTGCCCCGGC ACTTCGCCCA 3720

ATAGCAGCCA GTCCCTTCCC GCTTCAGTGA CAACGTCGAG CACAGCTGCG CAAGGAACGC 3780

CCGTCGTGGC CAGCCACGAT AGCCGCGCTG CCTCGTCTTG CAGTTCATTC AGGGCACCGG 3840

ACAGGTCGGT CTTGACAAAA AGAACCGGGC GCCCCTGCGC TGACAGCCGG AACACGGCGG 3900
CATCAGAGCA GCCGATTGTC TGTTGTGCCC AGTCATAGCC GAATAGCCTC TCCACCCAAG 3960

CGGCCGGAGA ACCTGCGTGC AATCCATCTT GTTCAATCAT GCGAAACGAT CCTCATCCTG 4020

TCTCTTGATC GATCTTTGCA AAAGCCTAGG CCTCCAAAAA AGCCTCCTCA CTACTTCTGG 4080

AATAGCTCAG AGGCCGAGGC GGCCTCGGCC TCTGCATAAA TAAAAAAAAT TAGTCAGCCA 4140

TGGGGCGGAG AATGGGCGGA ACTGGGCGGA GTTAGGGGCG GGATGGGCGG AGTTAGGGGC 4200

GGGACTATGG TTGCTGACTA ATTGAGATGC ATGCTTTGCA TACTTCTGCC TGCTGGGGAG 4260

CCTGGGGACT TTCCACACCT GGTTGCTGAC TAATTGAGAT GCATGCTTTG CATACTTCTG 4320

CCTGCTGGGG AGCCTGGGGA CTTTCCACAC CCTAACTGAC ACACATTCCA CAGCTGGTTC 4380

TTTCCGCCTC AGGACTCTTC CTTTTTCAAT ATTATTGAAG CATTTATCAG GGTTATTGTC 4440

TCATGAGCGG ATACATATTT GAATGTATTT AGAAAAATAA ACAAATAGGG GTTCCGCGCA 4500

CATTTCCCCG AAAAGTGC 4518

(2) INFORMATION FOR SEQ ID NO:27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 25 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:

CTCCACATAG AGATATAGAC TTCTG 25

(2) INFORMATION FOR SEQ ID NO:28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 45 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:

CGATCTTATT AATTAACTGG AGTTTTGAGC CCRMCCCCTC CCATC 45

(2) INFORMATION FOR SEQ ID NO:29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5594 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:

TGCATTAGTT ATTAATAGTA ATCAATTACG GGGTCATTAG TTCATAGCCC ATATATGGAG 60

TTCCGCGTTA CATAACTTAC GGTAAATGGC CCGCCTGGCT GACCGCCCAA CGACCCCCGC 120

CCATTGACGT CAATAATGAC GTATGTTCCC ATAGTAACGC CAATAGGGAC TTTCCATTGA 180

CGTCAATGGG TGGAGTATTT ACGGTAAACT GCCCACTTGG CAGTACATCA AGTGTATCAT 240

ATGCCAAGTA CGCCCCCTAT TGACGTCAAT GACGGTAAAT GGCCCGCCTG GCATTATGCC 300

CAGTACATGA CCTTATGGGA CTTTCCTACT TGGCAGTACA TCTACGTATT AGTCATCGCT 360

ATTACCATGG TGATGCGGTT TTGGCAGTAC ATCAATGGGC GTGGATAGCG GTTTGACTCA 420

CGGGGATTTC CAAGTCTCCA CCCCATTGAC GTCAATGGGA GTTTGTTTTG GCACCAAAAT 480

CAACGGGACT TTCCAAAATG TCGTAACAAC TCCGCCCCAT TGACGCAAAT GGGCGGTAGG 540

CGTGTACGGT GGGAGGTCTA TATAAGCAGA GCTGGTTTAG TGAACCGTCA GATCCGCGCC 600

AGTCCTCCGA TTGACTGAGT CGCCCGGGTA CCCGTGTATC CAATAAACCC TCTTGCAGTT 660

GCATCCGACT TGTGGTCTCG CTGTTCCTTG GGAGGGTCTC CTCTGAGTGA TTGACTACCC 720

GTCAGCGGGG GTCTTTCATT TGGGGGCTCG TCCGGGATCG GGAGACCCCT GCCCAGGGAC 780

CACCGACCCA CCACCGGGAG GTAAGCTGGC CAGCAACTTA TCTGTGTCTG TCCGATTGTC 840

TAGTGTCTAT GACTGATTTT ATGCGCCTGC GTCGGTACTA GTTAGCTAAC TAGCTCTGTA 900

TCTGGCGGAC CCGTGGTGGA ACTGACGAGT TCGGAACACC CGGCCGCAAC CCTGGGAGAC 960

GTCCCAGGAG GAACAGGGGA GGATCAGGGA CGCCTGGTGG ACCCCTTTGA AGGCCAAGAG 1020

ACCATTTGGG GTTGCGAGAT CGTGGGTTCG AGTCCCACCT CGTGCCCAGT TGCGAGATCG 1080

TGGGTTCGAG TCCCACCTCG TGTTTTGTTG CGAGATCGTG GGTTCGAGTC CCACCTCGCG 1140

TCTGGTCACG GGATCGTGGG TTCGAGTCCC ACCTCGTGTT TTGTTGCGAG ATCGTGGGTT 1200

CGAGTCCCAC CTCGCGTCTG GTCACGGGAT CGTGGGTTCG AGTCCCACCT CGTGCAGAGG 1260

GTCTCAATTG GCCGGCCTTA GAGAGGCCAT CTGATTCTTC TGGTTTCTCT TTTTGTCTTA 1320

GTCTCGTGTC CGCTCTTGTT GTGACTACTG TTTTTCTAAA AATGGGACAA TCTGTGTCCA 1380

CTCCCCTTTC TCTGACTCTG GTTCTGTCGC TTGGTAATTT TGTTTGTTTA CGTTTGTTTT 1440

TGTGAGTCGT CTATGTTGTC TGTTACTATC TTGTTTTTGT TTGTGGTTTA CGGTTTCTGT 1500

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TCAGATCAAC AGCTGCCCTT ACGTATCGAT GGATCCCTCG ACTAACTAAT AGCCCATTCT 1680

CCAAGGTCGA GCGGGATCAA TTCCGCCCCC CCCCTAACGT TACTGGCCGA AGCCGCTTGG 1740

AATAAGGCCG GTGTGCGTTT GTCTATATGT TATTTTCCAC CATATTGCCG TCTTTTGGCA 1800

ATGTGAGGGC CCGGAAACCT GGCCCTGTCT TCTTGACGAG CATTCCTAGG GGTCTTTCCC 1860

CTCTCGCCAA AGGAATGCAA GGTCTGTTGA ATGTCGTGAA GGAAGCAGTT CCTCTGGAAG 1920

CTTCTTGAAG ACAAACAACG TCTGTAGCGA CCCTTTGCAG GCAGCGGAAC CCCCCACCTG 1980

GCGACAGGTG CCTCTGCGGC CAAAAGCCAC GTGTATAAGA TACACCTGCA AAGGCGGCAC 2040

AACCCCAGTG CCACGTTGTG AGTTGGATAG TTGTGGAAAG AGTCAAATGG CTCTCCTCAA 2100

GCGTATTCAA CAAGGGGCTG AAGGATGCCC AGAAGGTACC CCATTGTATG GGATCTGATC 2160

TGGGGCCTCG GTGCACATGC TTTACATGTG TTTAGTCGAG GTTAAAAAAA CGTCTAGGCC 2220

CCCCGAACCA CGGGGACGTG GTTTTCCTTT GAAAAACACG ATAATAATCA TGGCTACAGG 2280

CTCCCGGACG TCCCTGCTCC TGGCTTTTGG CCTGCTCTGC CTGCCCTGGC TTCAAGAGGG 2340

CAGTGCCTTC CCAACCATTC CCTTATCCAG GCTTTTTGAC AACGCTATGC TCCGCGCCCA 2400

TCGTCTGCAC CAGCTGGCCT TTGACACCTA CCAGGAGTTT GAAGAAGCCT ATATCCCAAA 2460

GGAACAGAAG TATTCATTCC TGCAGAACCC CCAGACCTCC CTCTGTTTCT CAGAGTCTAT 2520

TCCGACACCC TCCAACAGGG AGGAAACACA ACAGAAATCC AACCTAGAGC TGCTCCGCAT 2580

CTCCCTGCTG CTCATCCAGT CGTGGCTGGA GCCCGTGCAG TTCCTCAGGA GTGTCTTCGC 2640

CAACAGCCTG GTGTACGGCG CCTCTGACAG CAACGTCTAT GACCTCCTAA AGGACCTAGA 2700

GGAAGGCATC CAAACGCTGA TGGGGAGGCT GGAAGATGGC AGCCCCCGGA CTGGGCAGAT 2760

CTTCAAGCAG ACCTACAGCA AGTTCGACAC AAACTCACAC AACGATGACG CACTACTCAA 2820

GAACTACGGG CTGCTCTACT GCTTCAGGAA GGACATGGAC AAGGTCGAGA CATTCCTGCG 2880

CATCGTGCAG TGCCGCTCTG TGGAGGGCAG CTGTGGCTTC TAGCTGCCCG GGTGGCATCC 2940

TGTGACCCCT CCCCAGTGCC TCTCCTGGCC CTGGAAGTTG CCACTCCAGT GCCCACCAGC 3000

CTTGTCCTAA TGTGTGTCAG TTAGGGTGTG GAAAGTCCCC AGGCTCCCCA GCAGGCAGAA 3060

GTATGCAAAG CATGCATCTC AATTAGTCAG CAACCAGGTG TGGAAAGTCC CCAGGCTCCC 3120

CAGCAGGCAG AAGTATGCAA AGCATGCATC TCAATTAGTC AGCAACCATA GTCCCGCCCC 3180

TAACTCCGCC CATCCCGCCC CTAACTCCGC CCAGTTCCGC CCATTCTCCG CCCCATGGCT 3240

GACTAATTTT TTTTATTTAT GCAGAGGCCG AGGCCGCCTC GGCCTCTGAG CTATTCCAGA 3300

AGTAGTGAGG AGGCTTTTTT GGAGGCCTAG GCTTTTGCAA AAAGCTTCAC GCTGCCGCAA 3360

GCACTCAGGG CGCAAGGGCT GCTAAAGGAA GCGGAACACG TAGAAAGCCA GTCCGCAGAA 3420

ACGGTGCTGA CCCCGGATGA ATGTCAGCTA CTGGGCTATC TGGACAAGGG AAAACGCAAG 3480

CGCAAAGAGA AAGCAGGTAG CTTGCAGTGG GCTTACATGG CGATAGCTAG ACTGGGCGGT 3540

TTTATGGACA GCAAGCGAAC CGGAATTGCC AGCTGGGGCG CCCTCTGGTA AGGTTGGGAA 3600

GCCCTGCAAA GTAAACTGGA TGGCTTTCTT GCCGCCAAGG ATCTGATGGC GCAGGGGATC 3660

AAGATCTGAT CAAGAGACAG GATGAGGATC GTTTCGCATG ATTGAACAAG ATGGATTGCA 3720

CGCAGGTTCT CCGGCCGCTT GGGTGGAGAG GCTATTCGGC TATGACTGGG CACAACAGAC 3780
AATCGGCTGC TCTGATGCCG CCGTGTTCCG GCTGTCAGCG CAGGGGCGCC CGGTTCTTTT 3840

TGTCAAGACC GACCTGTCCG GTGCCCTGAA TGAACTGCAG GACGAGGCAG CGCGGCTATC 3900

GTGGCTGGCC ACGACGGGCG TTCCTTGCGC AGCTGTGCTC GACGTTGTCA CTGAAGCGGG 3960

AAGGGACTGG CTGCTATTGG GCGAAGTGCC GGGGCAGGAT CTCCTGTCAT CTCACCTTGC 4020

TCCTGCCGAG AAAGTATCCA TCATGGCTGA TGCAATGCGG CGGCTGCATA CGCTTGATCC 4080

GGCTACCTGC CCATTCGACC ACCAAGCGAA ACATCGCATC GAGCGAGCAC GTACTCGGAT 4140

GGAAGCCGGT CTTGTCGATC AGGATGATCT GGACGAAGAG CATCAGGGGC TCGCGCCAGC 4200

CGAACTGTTC GCCAGGCTCA AGGCGCGCAT GCCCGACGGC GAGGATCTCG TCGTGACCCA 4260

TGGCGATGCC TGCTTGCCGA ATATCATGGT GGAAAATGGC CGCTTTTCTG GATTCATCGA 4320

CTGTGGCCGG CTGGGTGTGG CGGACCGCTA TCAGGACATA GCGTTGGCTA CCCGTGATAT 4380

TGCTGAAGAG CTTGGCGGCG AATGGGCTGA CCGCTTCCTC GTGCTTTACG GTATCGCCGC 4440

TCCCGATTCG CAGCGCATCG CCTTCTATCG CCTTCTTGAC GAGTTCTTCT GAGCGGGACT 4500

CTGGGGTTCG AAATGACCGA CCAAGCGACG CCCAACCTCC AGAAAAAGGG GGGAATGAAA 4560

GACCCCACCT GTAGGTTTGG CAAGCTAGCT TAAGTAACGC CATTTTGCAA GGCATGGAAA 4620

AATACATAAC TGAGAATAGA GAAGTTCAGA TCAAGGTCAG GAACAGATGG AACAGCTGAA 4680

TATGGGCCAA ACAGGATATC TGTGGTAAGC AGTTCCTGCC CCGGCTCAGG GCCAAGAACA 4740

GATGGAACAG CTGAATATGG GCCAAACAGG ATATCTGTGG TAAGCAGTTC CTGCCCCGGC 4800

TCAGGGCCAA GAACAGATGG TCCCCAGATG CGGTCCAGCC CTCAGCAGTT TCTAGAGAAC 4860

CATCAGATGT TTCCAGGGTG CCCCAAGGAC CTGAAATGAC CCTGTGCCTT ATTTGAACTA 4920

ACCAATCAGT TCGCTTCTCG CTTCTGTTCG CGCGCTTCTG CTCCCCGAGC TCAATAAAAG 4980

AGCCCACAAC CCCTCACTCG GGGCGCCAGT AATCTGCTGC TTGCAAACAA AAAAACCACC 5040

GCTACCAGCG GTGGTTTGTT TGCCGGATCA AGAGCTACCA ACTCTTTTTC CGAAGGTAAC 5100

TGGCTTCAGC AGAGCGCAGA TACCAAATAC TGTCCTTCTA GTGTAGCCGT AGTTAGGCCA 5160

CCACTTCAAG AACTCTGTAG CACCGCCTAC ATACCTCGCT CTGCTAATCC TGTTACCAGT 5220

GGCTGCTGCC AGTGGCGATA AGTCGTGTCT TACCGGGTTG GACTCAAGAC GATAGTTACC 5280

GGATAAGGCG CAGCGGTCGG GCTGAACGGG GGGTTCGTGC ACACAGCCCA GCTTGGAGCG 5340

AACGACCTAC ACCGAACTGA GATACCTACA GCGTGAGCAT TGAGAAAGCG CCACGCTTCC 5400

CGAAGGGAGA AAGGCGGACA GGTATCCGGT AAGCGGCAGG GTCGGAACAG GAGAGCGCAC 5460

GAGGGAGCTT CCAGGGGGAA ACGCCTGGTA TCTTTATAGT CCTGTCGGGT TTCGCCACCT 5520

CTGACTTGAG CGTCGATTTT TGTGATGCTC GTCAGGGGGG CGGAGCCTAT GGAAAAACGC 5580

CAGCAACGCC GAGA 5594

(2) INFORMATION FOR SEQ ID NO:30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6561 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:

GATCCCCGGG TCGACCCGGG TCGACCCTGT GGAATGTGTG TCAGTTAGGG TGTGGAAAGT 60

CCCCAGGCTC CCCAGCAGGC AGAAGTATGC AAAGCATGCA TCTCAATTAG TCAGCAACCA 120

GGTGTGGAAA GTCCCCAGGC TCCCCAGCAG GCAGAAGTAT GCAAAGCATG CATCTCAATT 180

AGTCAGCAAC CATAGTCCCG CCCCTAACTC CGCCCATCCC GCCCCTAACT CCGCCCAGTT 240

CCGCCCATTC TCCGCCCCAT GGCTGACTAA TTTTTTTTAT TTATGCAGAG GCCGAGGCCG 300

CCTCGGCCTC TGAGCTATTC CAGAAGTAGT GAGGAGGCTT TTTTGGAGGC CTAGGCTTTT 360

GCAAAAAGCT TCACGCTGCC GCAAGCACTC AGGGCGCAAG GGCTGCTAAA GGAAGCGGAA 420

CACGTAGAAA GCCAGTCCGC AGAAACGGTG CTGACCCCGG ATGAATGTCA GCTACTGGGC 480

TATCTGGACA AGGGAAAACG CAAGCGCAAA GAGAAAGCAG GTAGCTTGCA GTGGGCTTAC 540

ATGGCGATAG CTAGACTGGG CGGTTTTATG GACAGCAAGC GAACCGGAAT TGCCAGCTGG 600

GGCGCCCTCT GGTAAGGTTG GGAAGCCCTG CAAAGTAAAC TGGATGGCTT TCTTGCCGCC 660

AAGGATCTGA TGGCGCAGGG GATCAAGATC TGATCAAGAG ACAGGATGAG GATCGTTTCG 720

CATGATTGAA CAAGATGGAT TGCACGCAGG TTCTCCGGCC GCTTGGGTGG AGAGGCTATT 780

CGGCTATGAC TGGGCACAAC AGACAATCGG CTGCTCTGAT GCCGCCGTGT TCCGGCTGTC 840

AGCGCAGGGG CGCCCGGTTC TTTTTGTCAA GACCGACCTG TCCGGTGCCC TGAATGAACT 900

GCAGGACGAG GCAGCGCGGC TATCGTGGCT GGCCACGACG GGCGTTCCTT GCGCAGCTGT 960

GCTCGACGTT GTCACTGAAG CGGGAAGGGA CTGGCTGCTA TTGGGCGAAG TGCCGGGGCA 1020

GGATCTCCTG TCATCTCACC TTGCTCCTGC CGAGAAAGTA TCCATCATGG CTGATGCAAT 1080

GCGGCGGCTG CATACGCTTG ATCCGGCTAC CTGCCCATTC GACCACCAAG CGAAACATCG 1140

CATCGAGCGA GCACGTACTC GGATGGAAGC CGGTCTTGTC GATCAGGATG ATCTGGACGA 1200

AGAGCATCAG GGGCTCGCGC CAGCCGAACT GTTCGCCAGG CTCAAGGCGC GCATGCCCGA 1260

CGGCGAGGAT CTCGTCGTGA CCCATGGCGA TGCCTGCTTG CCGAATATCA TGGTGGAAAA 1320

TGGCCGCTTT TCTGGATTCA TCGACTGTGG CCGGCTGGGT GTGGCGGACC GCTATCAGGA 1380

CATAGCGTTG GCTACCCGTG ATATTGCTGA AGAGCTTGGC GGCGAATGGG CTGACCGCTT 1440

CCTCGTGCTT TACGGTATCG CCGCTCCCGA TTCGCAGCGC ATCGCCTTCT ATCGCCTTCT 1500

TGACGAGTTC TTCTGAGCGG GACTCTGGGG TTCGAAATGA CCGACCAAGC GACGCCCAAC 1560

CTGCCATCAC GAGATTTCGA TTCCACCGCC GCCTTCTATG AAAGGTTGGG CTTCGGAATC 1620
GTTTTCCGGG ACGCCGGCTG GATGATCCTC CAGCGCGGGG ATCTCATGCT GGAGTTCTTC 1680

GCCCACCCCG GAATTCGTAA TCTGCTGCTT GCAAACAAAA AAACCACCGC TACCAGCGGT 1740

GGTTTGTTTG CCGGATCAAG AGCTACCAAC TCTTTTTCCG AAGGTAACTG GCTTCAGCAG 1800

AGCGCAGATA CCAAATACTG TCCTTCTAGT GTAGCCGTAG TTAGGCCACC ACTTCAAGAA 1860

CTCTGTAGCA CCGCCTACAT ACCTCGCTCT GCTAATCCTG TTACCAGTGG CTGCTGCCAG 1920

TGGCGATAAG TCGTGTCTTA CCGGGTTGGA CTCAAGACGA TAGTTACCGG ATAAGGCGCA 1980

GCGGTCGGGC TGAACGGGGG GTTCGTGCAC ACAGCCCAGC TTGGAGCGAA CGACCTACAC 2040

CGAACTGAGA TACCTACAGC GTGAGCATTG AGAAAGCGCC ACGCTTCCCG AAGGGAGAAA 2100

GGCGGACAGG TATCCGGTAA GCGGCAGGGT CGGAACAGGA GAGCGCACGA GGGAGCTTCC 2160

AGGGGGAAAC GCCTGGTATC TTTATAGTCC TGTCGGGTTT CGCCACCTCT GACTTGAGCG 2220

TCGATTTTTG TGATGCTCGT CAGGGGGGCG GAGCCTATGG AAAAACGCCA GCAACGCCGA 2280

GATGCGCCGC CTCGAGTACA CCTGCGTCAT GCTGAGACCC TCAAGCCTCA CTAAAAGGGT 2340

CCCTGCCTAG TTCTGTTTAC TAATCTGCCT TATTCTGTTT TTGTTCCCAT GTTAAAGATA 2400

GAGTAAATGC AGTATTCTCC ACATAGAGAT ATAGACTTCT GAAATTCTAA GATTAGAATT 2460

ATTTACAAGA AGAAGTGGGG AATGAAGAAT AAAAAATTAC TGGCCTCTTG TGAGAACATG 2520

AACTTTCACC TCGGAGCCCA CCCCCTCCCA TCTGGAAAAC ATACTTGAGA AAAACATTTT 2580

CTGGAACAAC CACAGAATGT TTCAACAGGC CAGATGTATT GCCAAACACA GGATATGACT 2640

CTTTGGTTGA GTAAATTTGT GGTTGTTAAA CTTCCCCTAT TCCCTCCCCA TTCCCCCTCC 2700

CAGTTTGTGG TTTTTTCCTT TAAAAGCTTG TGAAAAATTT GAGTCGTCGT CGAGACTCCT 2760

CTACCCTGTG CAAAGGTGTA TGAGTTTCGA CCCCAGAGCT CTGTGTGCTT TCTGTTGCTG 2820

CTTTATTTCG ACCCCAGAGC TCTGGTCTGT GTGCTTTCAT GTCGCTGCTT TATTAAATCT 2880

TACCTTCTAC ATTTTATGTA TGGTCTCAGT GTCTTCTTGG GTACGCGGCT GTCCCGGGAC 2940

TTGAGTGTCT GAGTGAGGGT CTTCCCTCGA GGGTCTTTCA TTTGGTACAT GGGCCGGGAA 3000

TTCGAGAATC TTTCATTTGG TGCATTGGCC GGGAATTCGA AAATCTTTCA TTTGGTGCAT 3060

TGGCCGGGAA ACAGCGCGAC CACCCAGAGG TCCTAGACCC ACTTAGAGGT AAGATTCTTT 3120

GTTCTGTTTT GGTCTGATGT CTGTGTTCTG ATGTCTGTGT TCTGTTTCTA AGTCTGGTGC 3180

GATCGCAGTT TCAGTTTTGC GGACGCTCAG TGAGACCGCG CTCCGAGAGG GAGTGCGGGG 3240

TGGATAAGGA TAGACGTGTC CAGGTGTCCA CCGTCCGTTC GCCCTGGGAG ACGTCCCAGG 3300

AGGAACAGGG GAGGATCAGG GACGCCTGGT GGACCCCTTT GAAGGCCAAG AGACCATTTG 3360

GGGTTGCGAG ATCGTGGGTT CGAGTCCCAC CTCGTGCCCA GTTGCGAGAT CGTGGGTTCG 3420

AGTCCCACCT CGTGTTTTGT TGCGAGATCG TGGGTTCGAG TCCCACCTCG CGTCTGGTCA 3480

CGGGATCGTG GGTTCGAGTC CCACCTCGTG TTTTGTTGCG AGATCGTGGG TTCGAGTCCC 3540

ACCTCGCGTC TGGTCACGGG ATCGTGGGTT CGAGTCCCAC CTCGTGCAGA GGGTCTCAAT 3600
TGGCCGGCCT TAGAGAGGCC ATCTGATTCT TCTGGTTTCT CTTTTTGTCT TAGTCTCGTG 3660

TCCGCTCTTG TTGTGACTAC TGTTTTTCTA AAAATGGGAC AATCTGTGTC CACTCCCCTT 3720

TCTCTGACTC TGGTTCTGTC GCTTGGTAAT TTTGTTTGTT TACGTTTGTT TTTGTGAGTC 3780

GTCTATGTTG TCTGTTACTA TCTTGTTTTT GTTTGTGGTT TACGGTTTCT GTGTGTGTCT 3840

TGTGTGTCTC TTTGTGTTCA GACTTGGACT GATGACTGAC GACTGTTTTT AAGTTATGCC 3900

TTCTAAAATA AGCCTAAAAA TCCTGTCAGA TCCCTATGCT GACCACTTCC TTTCAGATCA 3960

ACAGCTGCCC TGCCTCCCAC TCCAACTCCA GAGAGCAGCC AGCGGGTCAC AGTGGTCCCG 4020

CCCATGAACC TGGAGCCTAG GGAAAAATGA GCTCGGAAAT CCGGAGCAAA TGAGGAGTGG 4080

TCCCTGAGAA GTCAGTGGCC TAAATGTTGT GGCTGCTGAA GCAAAAGAAG AGGAGGCTGT 4140

TCGAGTAGCC GGCCAAGAGC GCCGCGGGTT CCCAGGCAGC TTCTCATTCC CCTGTCCCTC 4200

CCATCCCGTC TCTTGTTAAC AGAAAAACTG CTTTCACTTT GAGATATGAG TGGCCCGATA 4260

CAGCCAGCTG TGAGAGCTGT ACTCCCTTCC CTGCCCCACG TGTTTTCTCT TCTCAGGCGA 4320

CCCCTCCCTG AGCTGCTGGC AGTGAGTCTG TTCTAAGCTC CAGTGAGGGA GGCATCCGCC 4380

CACTTGGGGC TTCTGTCCAA GGTAAGGAGC ACCTGTGAGT CTAACTGCCA GGCTCTGATG 4440

GGGGTCTCGT CTCTGTGGGA CTAGAAAGTG TCCCAACAAT CTGACCAAGG TAACAGGAAG 4500

TTAAGACAAA GACAGAGACC AAAGTCAGAA TCAGAGCTGT GCTGTGAGAC AAAAAGATAA 4560

AAAAAATAAA ATGCTGGCCA CAAAAGTCAG GAAAACTAGA AAACTTAGAT AGTACCTGGC 4620

AACAAAAGAA AGCTTTTGGC TAAAGATCAA CGTGTATACT GTAAAGAAAA TGAGCACTGG 4680

GTGAGAGACT GCCCCAACAA AAAGAAGAGG AGCCCCCCTC ATGACCAAAC CCTTCACCTG 4740

TTCGTGGCTA AAAGTAAAGA GATAACAAAA GGGGTGCTAA CACAGAAGCT GAGTCCTTAA 4800

AAGAGTCCGG TGGCCTACCT GTTGAAGCAG CTAAAAAAGA GACTGTGTTT CATACTCCTC 4860

CACTGACCAG TGCAAAACAA GCTAAAAAGT TCCTGGGCAC TGCGGGCTTT TGCAGATTGT 4920

GGATTCCAGG TTTTGCTGAG TTAAAGAGAT AAACAGCCCT TCGTATAGAA AAATAAAAAA 4980

CAACCTTGGA TGTCCTTGGA TGCTATTGAG ACTGCCCTAA TGTTGTCCCC AGCTATGGGA 5040

CTCCTAGATG TGACTGAGAA CAAAGGTATT GCCAAAGAAG TTCTTACTCA GAGATTGGGA 5100

CCCTGAAAAA GACCTGTGGC ATACTTGTAA GAAATTAGAC CTGGTGGCTG TAAGATGGCC 5160

TGCTTGTCTG CACATAGTGG CTTCTGGTCA AGGACGCAGA TAAATTGACT CTGAGACAAA 5220

ACTTGGCACA TGTCCTAGAA AGTGTGGTTC AGCCCCCATG ACCGATGGCT GACTAACGCT 5280

CTTGAAAACA TTATCCAACT GTTCCCCTGA CCGATGGACA CATTGTCAGA GCTTTTTTTG 5340

ACTGAACGAG TGACCTTCGC TCCCCCTGCT ATCCTCGATC TCACTACTGC CTGAGACTTC 5400

ACCTACTCAT CATTGTGCTG ACATTCTGGC AGAAGAAACT CATACTCGAA ATGATCTGAA 5460

GGATCAGATC AGCCTTGGCC TGAGAGTTTG AGCTGGTACA CGGATGGCAG TAGCCTGGAG 5520

GTTAAGGGTA AGCGGAAGGC GGGGACAGCA GTGCAGTGGT GGACAGAAAG CAAGTGATCT 5580
AGGCCAGCAG CCTCCCTAAA GGGACTTCAG CCCACAAAGC CAAACTTGTG GCTTTAATAC 5640

AAGCTCTGTA AATGGTAAAA AAAAAAAAGT CTACACGGAC AGCAGGTATG CTCTTGCCAC 5700

TGTACAGAGC AATATACAGA CAAAGAGAAC TGTTGACATC TGCAGAGAAA GACCTAAGAT 5760

GCTGTGGCTA AAAGAAATCA GATGGCAAAT CTAACCGCCC AGGCATCCTA AAGAGCAATG 5820

ATCCTGACAG TCTGAAGACT ATCAAGTTAT AGACAAATTA AGACTGGTAA AAAAAACCCT 5880

GTATAAAATA GTAAAAACTG AAAAAAGAAA ACTAGTCCTC TCATGAGAAG ACAGACCTGA 5940

CATCTACTGA AAAATAGACT TTACTGGAAA AAATATGTGT ATGAATACCT TCTAGTTTTT 6000

GTGAACGTTC TCAAGATGGA TAAAAGCTTT TCCTTGTAAA ACGAGACTGA TCAGATAGTC 6060

ATCAAGAAGA TTGTTAAAGA AAATTTTCCA AGGTTCGGAG TGCCAAAAGC AATAGTGTCA 6120

GATAATGGTC CTGCCTTTGT TGCCCAGGTA AGTCAGGGTG TGGCCAAGTA TTTAGAGGTC 6180

AAATGAAAAT TCCATTGTGT GTACAGACCT CAGAGCTCAG GAAAGATAAA AAAGAATAAA 6240

TAAAACTCTA AACAGACCTT GACAAAATTA ATCCTAGAGA CTGGCACAGA CTTACTTGGT 6300

ACTCCTTCCC CTTGCCCTAT TTAGAACTGA GAATACTCCC TCTTGATTCG GTTTTACTCT 6360

TTTTAAGATC CTTTATGGGG CTCCTATGCC ATCACTGTCT TAAATGATGT GTTTAAACCT 6420

ATGTTGTTAT AATAATGATC TATATGTTAA GTTAAAAGGC TTGCAGGTGG TGCAGAAAGA 6480

AGTCTGGTCA CAACTGGCTA CAGTGAACAA GCTGGGTACC CCAAGGACAT CTTACCAGTT 6540

CCAGCCAGAG ATCTGATCTA C 6561

(2) INFORMATION FOR SEQ ID NO:31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:

GACTAACCTT GATTCCACTG GAGCCGTATT ACCGCCATGC ATTAGTTATT AATAG 55

(2) INFORMATION FOR SEQ ID NO:32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:
GACTAACCTT GATTCCACTG GAGTAATTGC GGCTAGCGGA TCTGACG 47

(2) INFORMATION FOR SEQ ID NO:33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 66 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:

GACTAACCTT GATTCCACTG GAGACACTTG ACCTCTACCG CGCCAGTCCT CCGATTGACT 60

GAGTCG 66

(2) INFORMATION FOR SEQ ID NO:34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34:

GACTAACCTT GATTCCACTG GAGGGATCCG CGCCCATGAT TATTATCG 48

(2) INFORMATION FOR SEQ ID NO:35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

GACTAACCTT GATTCCAGCA ATGTCATGGC TACAGGCTCC CGGACGTCCC TGCTC 55

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs

(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

GACTAACCTT GATTCCAGCA ATGTTAGGAC AAGGCTGGTG GGCACTGG 48

(2) INFORMATION FOR SEQ ID NO:37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:

GACTAACCTT GATTCCACTG GAGGGTCGAC CCTGTGGAAT GTGTGTCAG 49

(2) INFORMATION FOR SEQ ID NO:38:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 48 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:

GACTAACCTT GATTCCACTG GAGAATCTCG TGATGGCAGG TTGGGCGT 48

(2) INFORMATION FOR SEQ ID NO:39:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 54 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:39:

GACTAACCTT GATTCCACTG AAGAGATTTT ATTTAGTCTC CAGAAAAAGG GGGG 54

(2) INFORMATION FOR SEQ ID NO:40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:40:

GACTAACCTT GATTCCACTG AAGCCCCCAA ATGAAAGACC CCCGCTGACG 50

(2) INFORMATION FOR SEQ ID NO:41:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 49 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:41:

GACTAACCTT GATTCCACTG GAGCCGGGAC GGAATTCGTA ATCTGCTGC 49

(2) INFORMATION FOR SEQ ID NO:42:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

GACTAACCTT GATTCCACTG GAGTTCTCGA GGCGGCGCAT CTCGGCG 47

(2) INFORMATION FOR SEQ ID NO:43:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

CGCTCTAGAA CTAGTGGATC 20

(2) INFORMATION FOR SEQ ID NO:44:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:44:

GTAATACGAC TCACTATAGG G 21

(2) INFORMATION FOR SEQ ID NO:45:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 43 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:45:

CGATCCACTG GAGCTCGGAG CCCACCCCCT CCCATCTAGA GGT 43

(2) INFORMATION FOR SEQ ID NO:46:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 43 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

CGTCCTCCTG GAGAGCACAG GGTAGAGGAG TCTCGACGGT CAG 43

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 43 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

CGCAACCCTG GAGACCTCTA GATGGGAGGG GGTGGGCTCC GAG 43

(2) INFORMATION FOR SEQ ID NO:48:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 43 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:48:

GCAGGACCTG GAGCTGACCG TCGAGACTCC TCTACCCTGT GCT 43

(2) INFORMATION FOR SEQ ID NO:49:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 20 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:49:

CGCTCTAGAA CTAGTGGATC 20

(2) INFORMATION FOR SEQ ID NO:50:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 21 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:50:

GTAATACGAC TCACTATAGG G 21

(2) INFORMATION FOR SEQ ID NO:51:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:51:

TACGTATCGA TGGATCCGA 19

(2) INFORMATION FOR SEQ ID NO:52:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 19 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:52:

GGATCCATCG ATACGTAAG 19

(2) INFORMATION FOR SEQ ID NO:53:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:

GGCCGCTAAC TAATAGCCCA TTCTCCAAGG TACGTAGC 38

(2) INFORMATION FOR SEQ ID NO:54:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 38 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:54:

TACGTACCTT GGAGAATGGG CTATTAGTTA GCGGCCGC 38

(2) INFORMATION FOR SEQ ID NO:55:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 55 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:
GACTAACCTT GATTCCACTG GAGTTTTCTC TATTCTTCAT TCCCCACTTC TTCTT 55

(2) INFORMATION FOR SEQ ID NO:56:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 60 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:56:

GACTAACCTT GATTCCACTG GAGAATCTGG ACCAATTCTA TATAAGCCTG TGAAAAATTT 60

(2) INFORMATION FOR SEQ ID NO:57:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:57:

GACTAACCTT GATTCCACTG GAGAAGAAGA AGTGGGGAAT GAAGAA 46

(2) INFORMATION FOR SEQ ID NO:58:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:58:

GACTAACCTT GATTCCACTG GAGATCTCTA GATGGGAGGG GGTCTGGGCT C 51

(2) INFORMATION FOR SEQ ID NO:59:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:59:

GACTAACCTT GATTCCACTG GAGCTCGGAG CCCACCCCCT CCCATCT 47

(2) INFORMATION FOR SEQ ID NO:60:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:60:

GACTAACCTT GATTCCACTG GAGGGAGGCC CTTATCTCAA AAATGTT 47

(2) INFORMATION FOR SEQ ID NO:61:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 51 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

GACTAACCTT GATTCCACTG GAGTCTAAGA ACATTTTTGA GATAAGGGCC T 51

(2) INFORMATION FOR SEQ ID NO:62:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:62:

GACTAACCTT GATTCCACTG GAGTCACAGG CTTATATAGT GAAA 44

(2) INFORMATION FOR SEQ ID NO:63:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 46 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:63:

GACTAACCTT GATTCCCTGG AGACTGCACT GCTGTCCCCG CCTTCG 46

(2) INFORMATION FOR SEQ ID NO:64:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 53 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:64:

GAGTAACCTT GATTCCCTGG AGATTTCTCA GACCCGGGTC GACCCTGTGG AAT 53

(2) INFORMATION FOR SEQ ID NO:65:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 44 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:65:

GACTAACCTT GATTCCCTGG AGCTCGAGGC GGCGCATCTC GGCG 44

(2) INFORMATION FOR SEQ ID NO:66:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 47 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

GACTAACCTT GATTCCCTGA AGACCTGCGT CATGCTGAGA CCCTCAA 47

(2) INFORMATION FOR SEQ ID NO:67:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:67:

GACTAACCTT GATTCCCTGA AGCGGCCAAT GCACCAAATG AAAGATTTTC 50

(2) INFORMATION FOR SEQ ID NO:68:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 50 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: DNA (genomic)

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

CGCATCTTTT AATTAACTGG AGARAATTTT TYACAGGCTT ATATAGKAAA 50

We claim:

1. A method for assembling a gene or gene vector comprising the steps of:

a) designing at least 6 primers to produce at least three fragments in at least three separate polymerase chain reactions wherein each primer comprises at least one predetermined restriction endonuclease recognition site that recognizes a restriction endonuclease that cleaves at a distance from the recognition site, a sequence complementary to a template sequence for amplification, and bases positioned at the restriction endonuclease cleavage site that are selected to be complementary to only one other overhanging created from enzymatic cleavage of the fragments;

b) combining the primers with template nucleic acid and performing a gene amplification reaction to produce multiple copies of an amplified template fragment incorporating the restriction endonuclease recognition site;

c) digesting the amplified template fragments with one or more restriction endonucleases that recognize the restriction endonuclease recognition site of the primers to create overhanging termini wherein each overhanging termini is complementary to only one other overhanging termini on another fragment; and

d) combining the amplified and digested template fragments in a ligation reaction to produce a directionally ordered gene, nucleic acid fragment or gene vector.

2. The method of claim 1 wherein the restriction endonuclease is at least one class IIS restriction endonuclease.

3. The method of claim 2 wherein the class IIS restriction endonuclease is selected from the group consisting of: *Alw*I, *Alw*26I, *Bbs*I, *Bbv*I, *Bbv*II, *Bpm*I, *Bsm*AI, *Bsm*I, *Bsm*BI, *Bsp*MI, *Bsr*I, *Bsr*DI, *Eco*57I, *Ear*I, *Fok*I, *Gsu*I, *Hga*I, *Hph*I, *Mbo*II, *Mnl*I, *Ple*I, *Sap*I, *Sfa*NI, TaqII, *Tth*111II.

4. The method of claim 1 wherein class II restriction endonuclease recognition sites, linkers, or adapters are not used to create the gene or gene vector.

5. The method of claim 1 wherein the product of the ligation reaction is introduced into prokaryotic or eukaryotic cells.

6. The method of claim 1 wherein at least one target nucleic acid sequence is chosen from the group consisting of : transcriptional regulatory sequences; genetic vectors; introns and/or exons; viral encapsidation sequences; integration signals intended for introducing nucleic acid molecules into other nucleic acid molecules; retrotransposon(s); VL30 elements; or multiple allelic forms of a sequence.

7. The method of claim 1 wherein the method is used to generate combinatorial libraries of a target sequence.

8. The method of claim 7 wherein the target sequence is part or all of a gene.

9. The method of claim 8 wherein the gene encodes a protein.

10. The method of claim 8 wherein the primers amplify allelic variants of part or all of a gene.

11. The method of claim 1 wherein the product of the ligation reaction is passed between eukaryotic cells using a virus particle, by cell fusion, or by transfection.

12. The method of claim 1 wherein the product of the ligation reaction is not introduced into prokaryotic cells.

13. The method of claim 1 further combining at least one screening or selection step to select the products of the ligation reaction.

14. The method of claim 1 wherein the product of the ligation reaction is mutated during passage in cells in order to generate genetic diversity.

15. The method of claim 14 wherein the product of the ligation reaction is mutated by-homologous recombination during passage in cells.

16. The method of claim 1, wherein the method is used to isolate and identify regulatory sequences from a cell.

17. The method of claim 11, wherein cells containing the product of the ligation reaction are selected for enhanced biological activity.

18. The method of claim 17, wherein the cells containing the product of the ligation reaction are selected for tissue-specific, hormone-specific or developmental-specific gene expression.

19. The method of claim 1 wherein the product of the ligation reaction is a circularized gene vector.

20. A nucleic acid primer having a 5' and a 3' end to amplify a nucleic acid fragment for the ligation of at least two fragments comprising:

a restriction endonuclease recognition site that recognizes a restriction endonuclease, wherein the restriction endonuclease cleaves at a distance from the recognition site and creates overhanging termini;

a sequence complementary to a template sequence to be amplified to produce the nucleic acid fragment;

at least two nucleic acid bases positioned at the restriction endonuclease cleavage site and that form an overhanging terminus after cleavage by the restriction endonuclease, wherein the at least two nucleic acid bases are selected to be complementary to only one other overhanging terminus on another fragment of the ligation; and

an affinity handle on the 5' end of the primer.

21. The primer of claim 20 further comprising an anchor to provide stability to the restriction enzyme at the restriction enzyme recognition site.

22. A method for isolating and identifying promoters comprising the steps of:

a) obtaining a vector comprising at least a portion of a promoter region from a retrovirus transposon LTR and having two non-complementary overhanging termini;

b) designing at least two PCR primers to amplify at least one region of a retro-transposon LTR from template nucleic acid to produce at least one nucleic acid fragment wherein each primer comprises at least one predetermined restriction endonuclease recognition site that recognizes a restriction endonuclease that cleaves at a distance from the recognition site, a sequence complementary to a template sequence from a retrovirus transposon, and bases positioned at the restriction endonuclease cleavage site that are selected to be complementary to only one other overhanging terminus of the vector wherein the restriction endonuclease cleavage site is created from enzymatic cleavage of the fragments;

c) combining the primers with template nucleic acid and performing a gene amplification reaction to produce multiple copies of an amplified template fragment incorporating the restriction endonuclease recognition site;

d) digesting the amplified template fragments with one or more restriction endonuclease that recognize the restriction endonuclease recognition site of the primer to create overhanging termini; and

e) combining the amplified and digested template fragment in a ligation reaction with the vector to produce a gene vector with an intact LTR sequence.

23. The method of claim 22 wherein the template nucleic acid is DNA or RNA.

24. The method of claim 22 further comprising the step of sequencing the insert to identify the promoter sequence.

25. Promoter sequences of SEQ ID NOS:2-13 identified using the methods of claim 22.

26. The vector of SEQ ID NO:1.

Fig 1A

A.

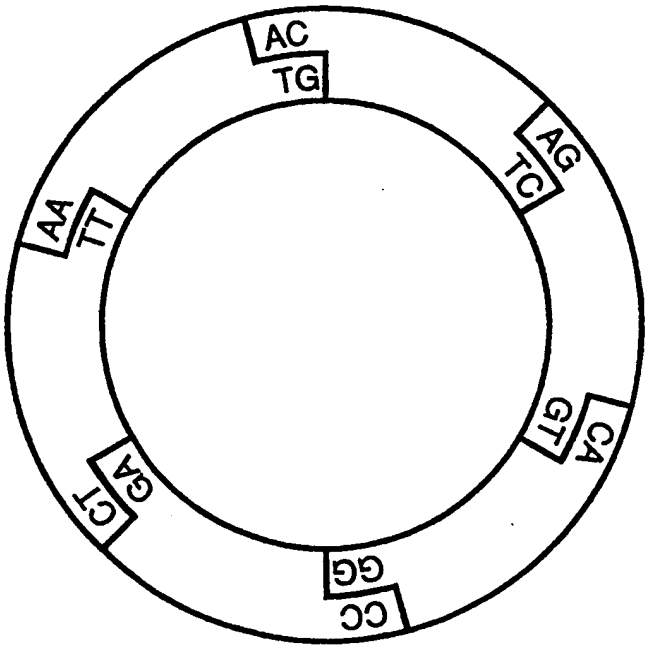
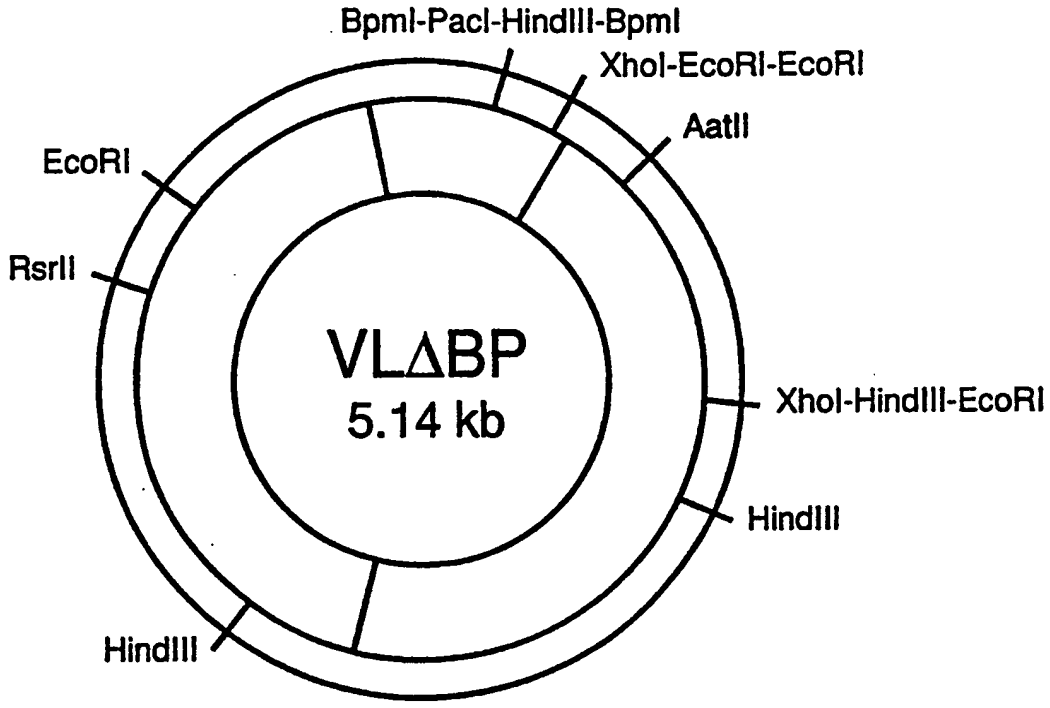


Fig 1B

B.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AatII
EcoRI
RsrII
VLΔBP
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XhoI-HindIII-EcoRI
HindIII
HindIII

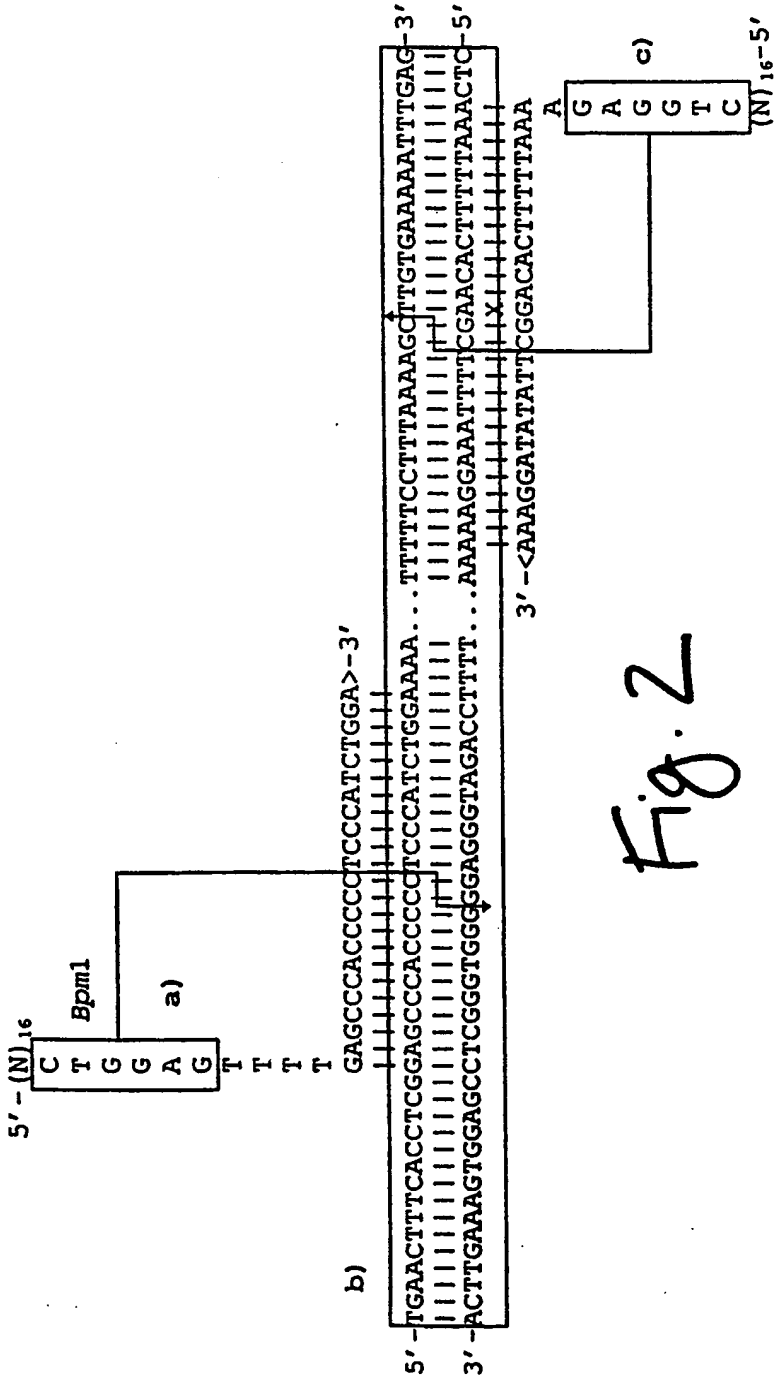
5'-(N)16
CTGGAG
Bpml
a)
TTTT
GAGCCCACCCCCTCCCATCTGGA>-3'
b)
5'-TGAACTTTCACCTCGGAGCCCACCCCCTCCCATCTGGAAAA...TTTTTCCTTTAAAAGCTTGTGAAAAATTTGAG-3'
3'-ACTTGAAAGTGGAGCCTCGGGTGGGGGGAGGGTAGACCTTTT...AAAAAGGAAATTTTCGAACACTTTTTAAACTC-5'
3'-<AAAGGATATATTCGGACACTTTTTAAA
A
GAGGTC
c)
(N)16-5'

Fig. 2

Fig. 3

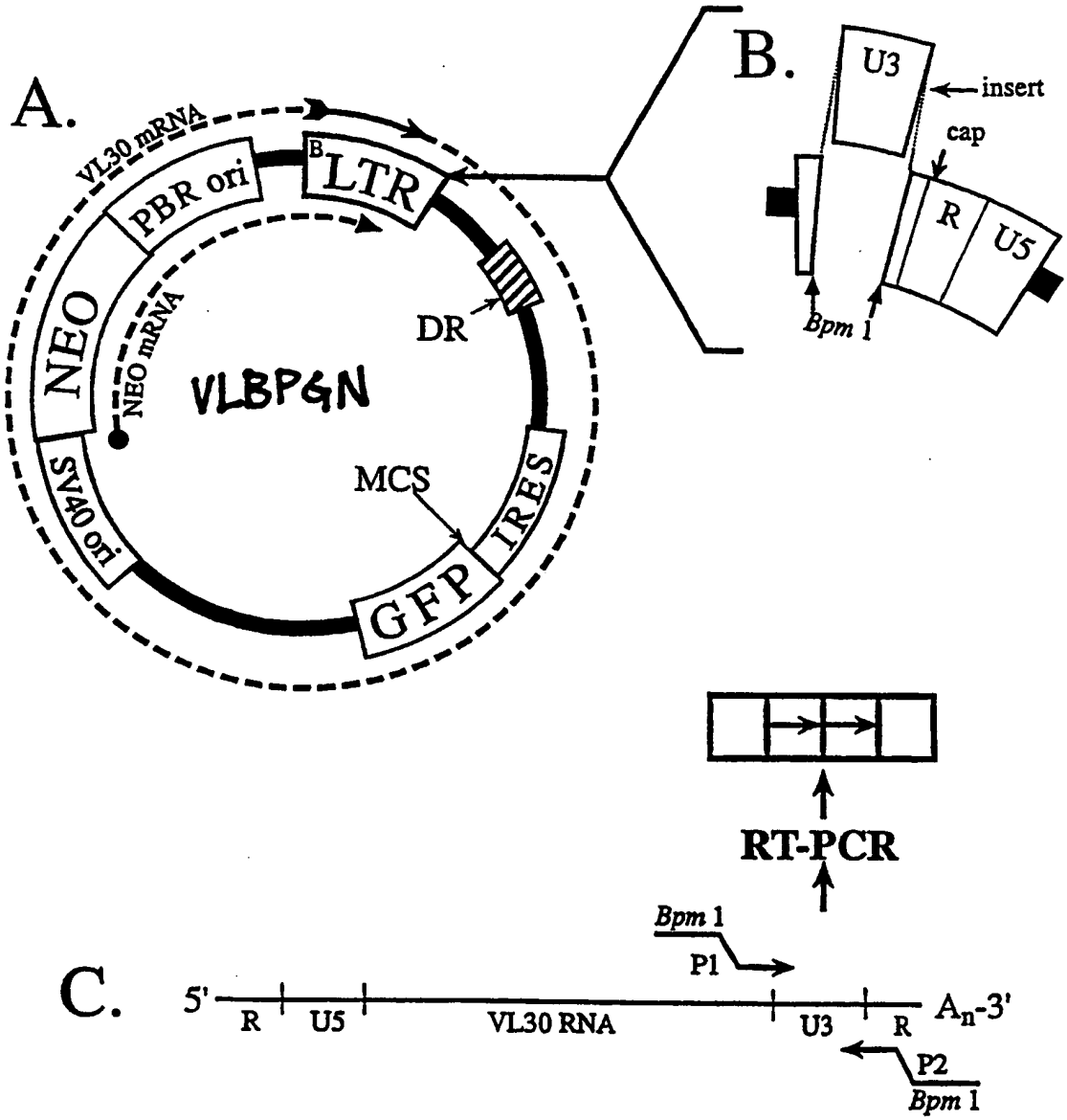
A.
VL30 mRNA
PBR ori
B
LTR
NEO
NEO mRNA
DR
VLBPGN
MCS
SV40 ori
IRES
GFP
B.
U3
insert
cap
R
U5
Bpm 1
RT-PCR
Bpm 1
P1
C.
5'
R
U5
VL30 RNA
U3
R
An-3'
P2
Bpm 1

Fig. 4 A.

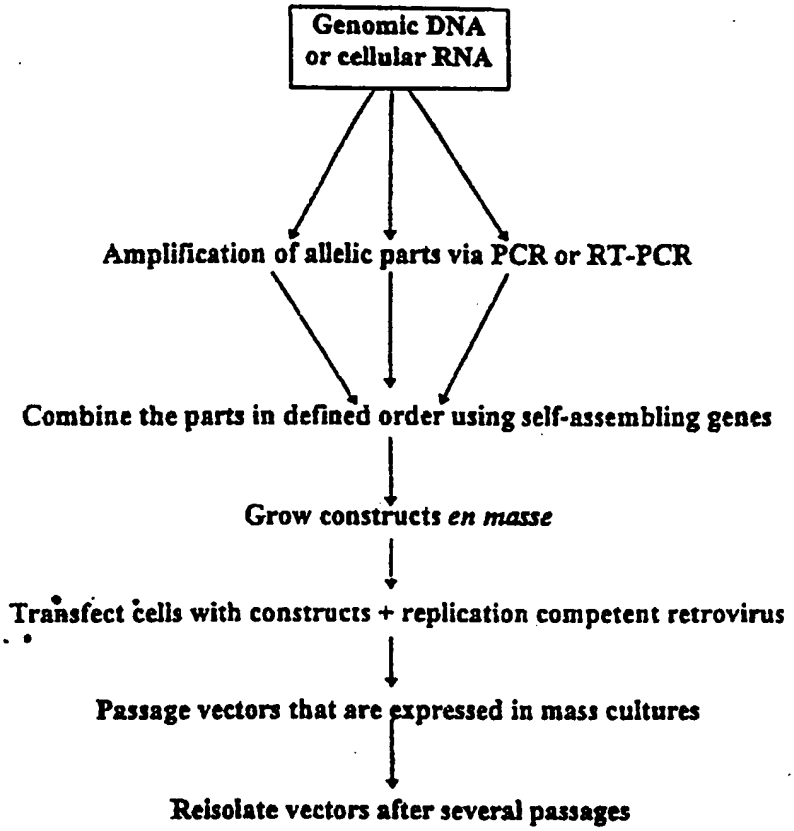
Genomic DNA or cellular RNA
Amplification of allelic parts via PCR or RT-PCR
Combine the parts in defined order using self-assembling genes
Grow constructs *en masse*
Transfect cells with constructs + replication competent retrovirus
Passage vectors that are expressed in mass cultures
Reisolate vectors after several passages

Fig 4 B.

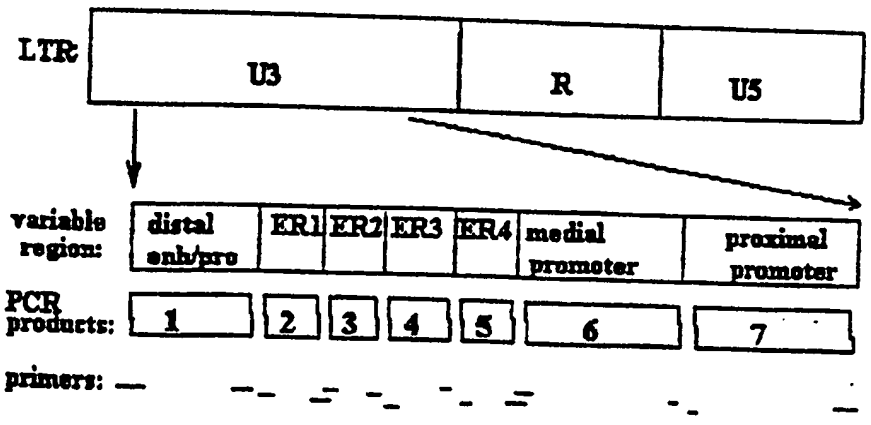
LTR:
U3
R
U5
variable region:
distal enh/pro
ER1
ER2
ER3
ER4
medial promoter
proximal promoter
PCR products:
1
2
3
4
5
6
7
primers:

Fig. 5

```
          1                                                                                                  90
I.D.2 CCTCCCATCT AGAGGTTGTT CTCGGAACAC TCCTAAACTT TTCACCCCAA AACTCCTCAC CCTAAAGTTC GAAAAAACTG TTCCAAGAAC
I.D.3 ---------- ---------- ---------- ---------- ---------- ---------- ---------- ---------- ----------

         91                                                                                                 180
I.D.2 ATTTTTGAGA TAAAGGCCTC CTAGAACAAC CTCAAAATGA CATTGCCAAA TGATAAGACA TGACTCCTTA GTTACGTAGG TTCCTTGATA
I.D.3 ---------- ---------- ---------- ---CCTCCCA TCTAGAAAAC ATTTTTGAGA TAAAGGCTTC CTGGAACAAC CTCAAAATGA

        181                                                                                                 270
I.D.2 GGACATGACT CCTTAGTTAC GTAGGTTCCT TGATAGGACA TGACTCCTTA GTTACGTAGA TTCCTTTGGT AGAACTCCCT AGTGATGTAA
I.D.3 ACCAGGTACT CCTTAGTTAC GTAGGTTCCT TGATAGGACA TGACTCCTTA GTTACATAGA TTCCTTTGGC AGAACTCCCT AGTGATGTAA

        271                                                 321
I.D.2 ACTTGTACTT TCCCTGCCCA GTTCTCCCCC TTTGAGTTTT ACTATATAAG C
I.D.3 ACTTGTACTT TCCCTGCCCA GTTCTCCCCC TTTGAGTTTT ACTATATAAG C
```

Fig. 6

```
     1                                                                                                  90
4    CCTCCCATCT AGAGATTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATGCC TGAACTCCTC ACCCTAGAGT TCGAACCCTC
5    CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC TGAACTCCTC ACCCTAGAGT TCGAACCCTC
6    CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC TGAACTCCTC ATCCTAGAGT TCGAACCCTC
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9    CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC TGAACCCCTC ACCCTAGAGT TCGAACCCTC
10   CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCATCCCAG AATGCATTCC TGAACTCCTC ACCCTATAGT TCGAACCCTC
11   CCTCCCATCT AGAGAGTGTT CCCAAAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC TGAACTCCTC ACCCTAAAGT TCAAACCCTC
12   CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTGAACTC TTCACCCCAG AATGCATTCC TGAACTCCTC ACCCTAGAGT TTGAACCCTC
13   CCTCCCATCT AGAGAGTGTT CCCAGAACAC TCCTAAACTC TTCACCCCAG AATGCATTCC TGAACTCCTC ACCCTAGAGT TCGAACCCTT

     91                                                                                                 180
4    CCAACTAAAG ACTGTTCCAA GAACATTTTT GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGG TACATTGCCA AATAATAGGA
5    CCAACTAAAG ACTGTTCCAA GAACATTTTT GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGA TACATTGCCA AATAATAGGA
6    CCAACTAAAG ACTGTTCCAA GAACATTTTT GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCTGG TACATTGCCA AATAATAGGA
7    CCAACTAAAG ACTGTTCCAA GAACATTTTT GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCAGG TACATTGCCA AATAATAGGA
8    CCAACTAAAG ACTGTTCCAA GAACATTTTT GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGA TACATTGCCA AATAATAGGA
9    CCAACTAAAG ACTGTTCCAA GAACATTTTT GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCAGG TACATTGCCA AATAATAGGA
10   CCAACTAAAG ACTGTTCCAA GAACATTTTT GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGG TACATTGCCA AATAATAGGA
11   CCAACTAAAG ACTGTTCCAA GAACATTTTT GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGG TACATTGCCA AATAATAGGA
12   CCAACTAAAG ACTGTTCCAA GAACATCTTT GAGATAAGGG CCTCCTGGAA CAACCTCAGA ATGAACCGGG TACATTGCCA AATAATAGGA
13   CCAACTAAAG ACTGTTCCAA GAACATTTTT GAGATAAGGG CCTCCTGGAA CAACCTCAAA ATGAACCGGG TACATTGCCA AATGATAGGA
```

Fig. 7

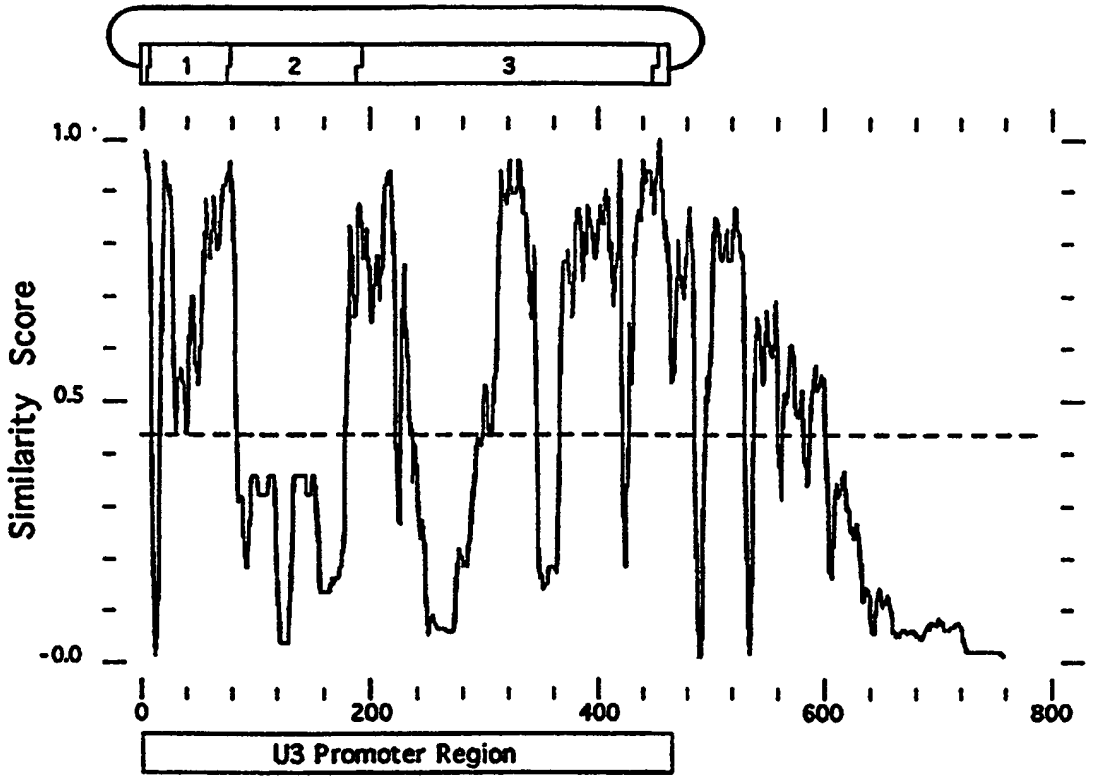
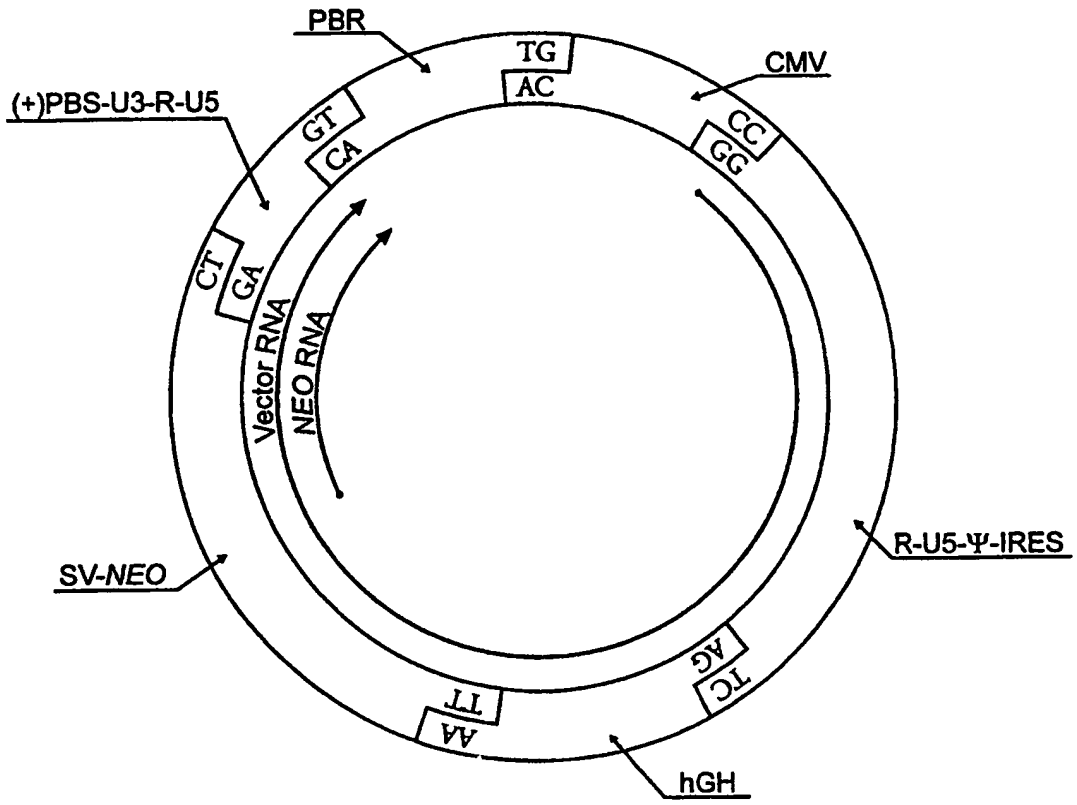

1
2
3
1.0
0.5
-0.0
Similarity Score
0
200
400
600
800
U3 Promoter Region

Fig. 8


PBR
TG
AC
CMV
(+)PBS-U3-R-U5
GT
CA
CC
GG
CT
GA
Vector RNA
NEO RNA
SV-NEO
R-U5-Ψ-IRES
AG
TC
TT
AA
hGH

INTERNATIONAL SEARCH REPORT

I. ational Application No
PCT/US 98/03918

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/86 C12N15/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PADGETT K A ET AL: "Creating seamless junctions independent of restriction sites in PCR cloning" GENE, vol. 168, no. 1, 2 February 1996, page 31-35 XP004042930	1,2, 4-14, 19-21
Y	see the whole document ---	3
Y	TOMIC, M. ET AL.: "A rapid and simple method for introducing specific mutations into any position of DNA leaving all other positions unaltered" NUCLEIC ACIDS RESEARCH. vol. 18, no. 6, 1990, OXFORD GB. page 1656 XP002069445 cited in the application see the whole document ---	3
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 June 1998	09/07/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chambonnet, F

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/US 98/03918

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	LEBEDENKO, E.N. ET AL.: "Method of artificial DNA splicing by directed ligation" NUCLEIC ACIDS RESEARCH, vol. 19, no. 24, 1991, OXFORD GB, pages 6757-6761, XP002069446 cited in the application see the whole document	1
A	CHAKRABORTY, A.K. ET AL.: "Synthetic retrotransposon vectors for gene therapy" FASEB JOURNAL., vol. 7, no. 10, July 1993, FOR EXPERIMENTAL BIOLOGY, BETHESDA, MD US, pages 971-977, XP002029486 see the whole document	1
P,X	WO 97 28282 A (STRATAGENE INC) 7 August 1997	1,2, 4-14, 19-21
P,Y	see the whole document	3
P,X	HODGSON, C.P. ET AL.: "Self-assembling genes (SAGE) : construction of complex vectors and combinatorial libraries without sub-cloning" CANCER GENE THERAPY, vol. 4, no. 6 conf. suppl., November 1997, page s27 XP002069448 see the whole document	1
P,X	ZINK, A. M. ET AL.: "Transcriptional targeting with rescued LTRs : a hepatocyte promoter" CANCER GENE THERAPY, vol. 4, no. 6 conf. suppl., November 1997, page s28 XP002069449 see the whole document	22

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 98/03918

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9728282 A	07-08-1997	NONE	